Vol. 28 No. 8 August 1977

Journal of the Society of Cosmetic Chemists

Contents

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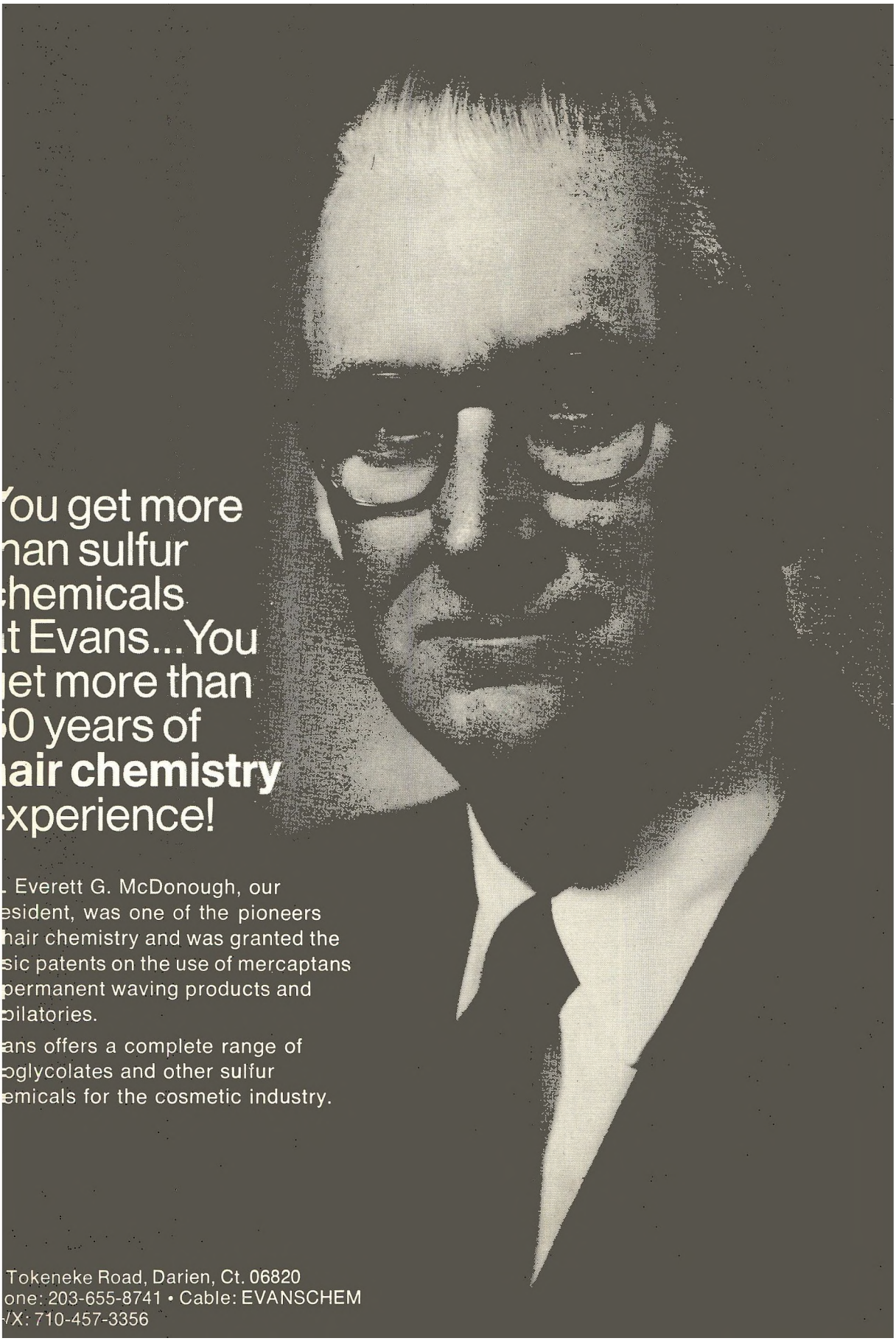
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Journal of the Society of Cosmetic Chemists

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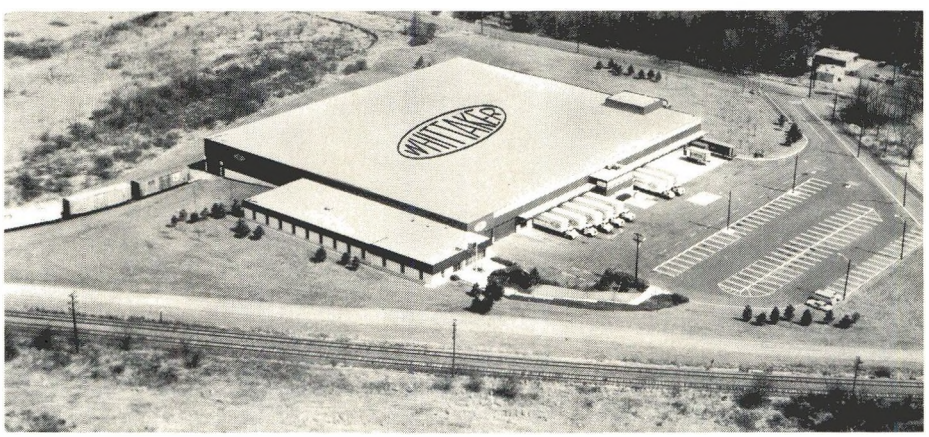

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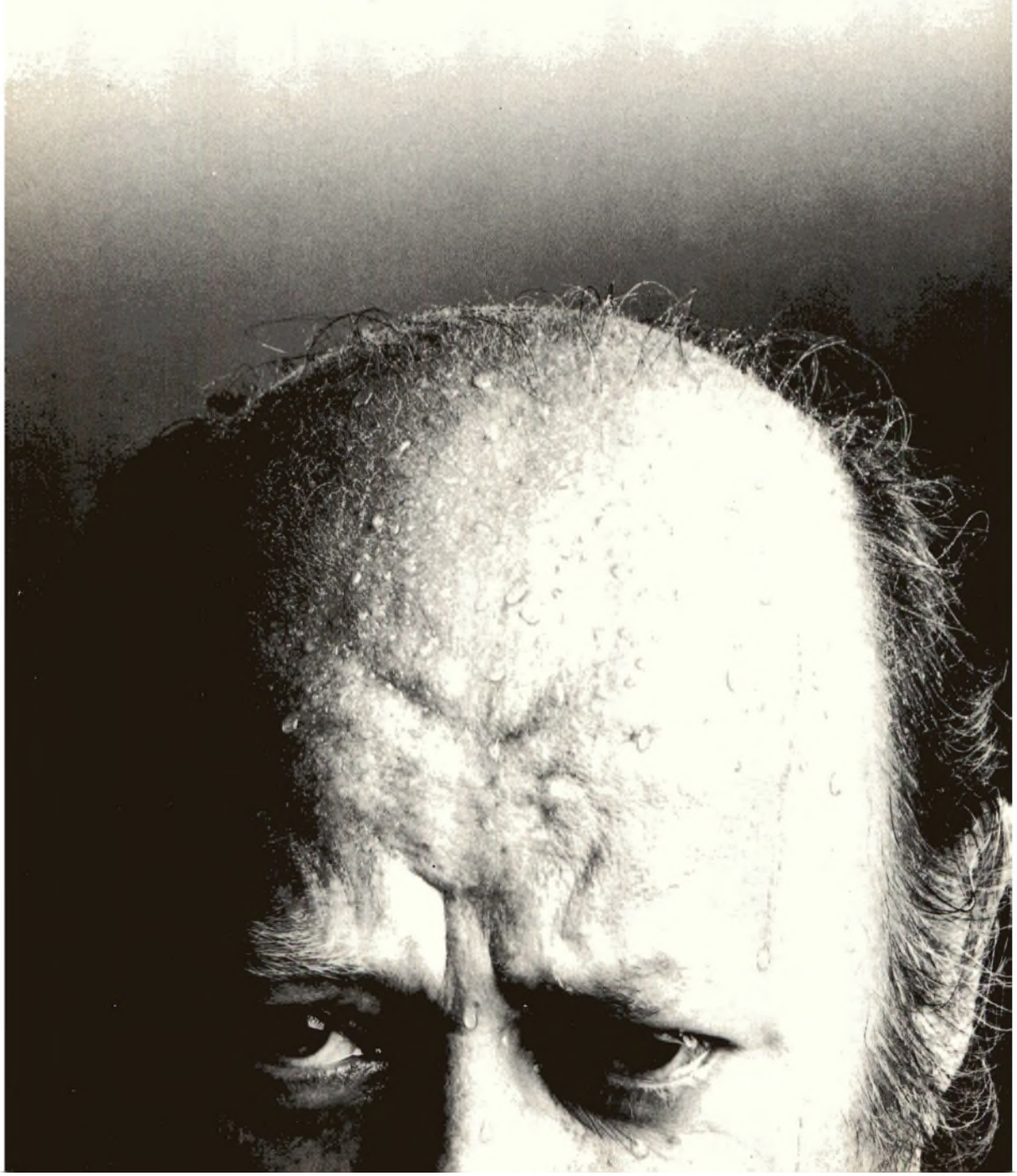

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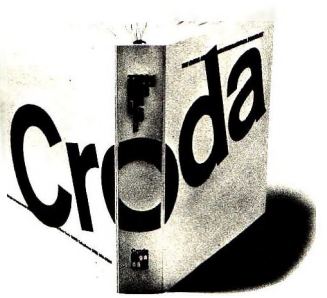

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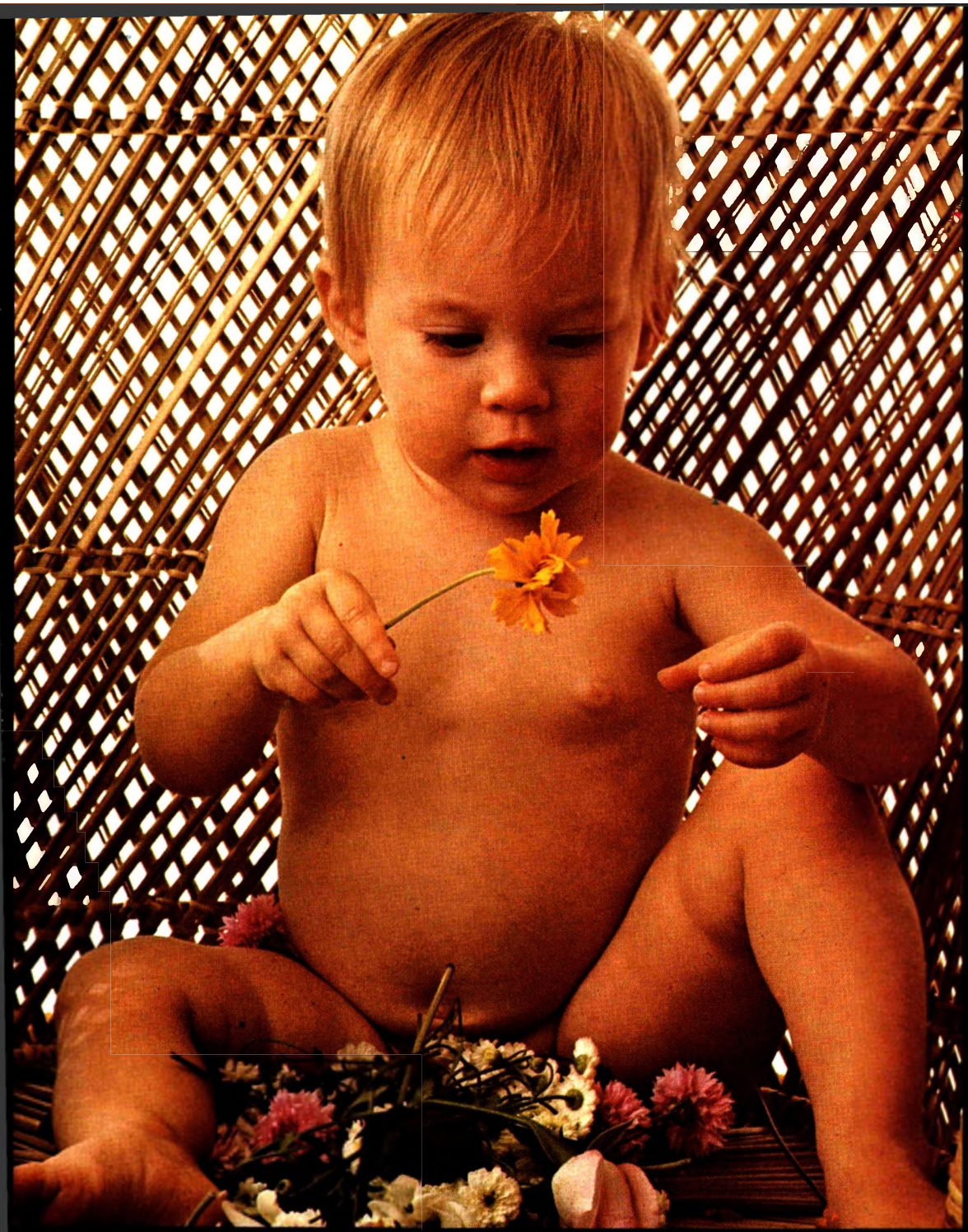

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SYNOPSES FOR CARD INDEXES

The following synopses can be cut out and mounted on 3 × 5 index cards for reference, without mutilating the pages of the Journal.

The physical properties of fingernails I. Apparatus for physical measurements: Michael J. Maloney, Elmer G. Paquette, and Albert Shansky. *Journal of the Society of Cosmetic Chemists* **28,** 415 (August 1977)

Synopsis—Miniature apparatus for measuring the physical properties of fingernails have been developed and tested. Included are a device for cutting test specimens; a template for preparing tensile bar samples; apparatus for performing flexural, tensile, and tearing tests; and a device for determining impact absorption. Whenever possible, methods were based on standard testing procedures so that recognized interpretative formulae could be used for analyzing experimental results. The range of physical properties found for the fingernails tested are as follows: flexural strength 4,928 to 17,653 psi; tensile strength 4,464 to 17,081 psi; tearing resistance 274.3 to 676.2 lb/in. and impact absorption (rebound ratio) 0.4632 to 0.7273.

5-Brom-5-nitro-1,3-dioxan-A new preservative for cosmetics: Peter Lorenz. *Journal of the Society of Cosmetic Chemists* 28, 427 (August 1977)

Synopsis—Bronidox®, a new preservative, is 5-bromo-5-nitro-1,3-dioxane. In concentrations of 0.02 to 0.05% it is active against gram-positive and gram-negative bacteria as well as fungi. Toxicological and dermatological investigations demonstrate that the compound is tolerated without adverse reactions. Attempts to produce sensitization reactions failed. This compound is currently recommended for the preservation of shampoos and foam baths.

Antiperspirant efficacy: E. S. Bretschneider, A. M. Rubino, and J. J. Margres. *Journal of the Society of Cosmetic Chemists* **28,** 441 (August 1977)

Synopsis—Antiperspirant efficacy of aluminum chlorohydrate "type" ingredients is discussed. The optimal efficacy for aluminum chlorohydrate and aluminum bromohydrate in aqueous solution occurs at concentrations of 15 per cent (3.75 per cent Al) and 24 per cent (5.0 per cent Al), respectively. No difference in efficacy between aluminum chlorohydrate-$AlCl_3$ combinations and aluminum chlorohydrate alone, is found. Efficacy differences are observed as a function of vehicle. For example, aqueous formulations appear to be more efficacious than anhydrous formulations. Efficacy of aluminum-zirconium compounds is discussed in terms of variation of Al:Zr ratio. No differences are found.

Studies on the molecular weight distribution of cosmetic protein hydrolysates: Elaine S. Stern and Vernon L. Johnsen. *Journal of the Society of Cosmetic Chemists* 28, 447 (August 1977)

Synopsis—Molecular weight has been thought to be an important feature of cosmetic grade pro-

teins and to be a critical factor affecting protein substantivity to hair. The study reported in this paper was undertaken to show the relationship of molecular weight to protein substantivity. Using gel filtration and ultracentrifugation data were obtained that indicate peptides in the range of molecular weight 1000 are more substantive than the very high molecular weight molecules.

Prediction of optimum O/W emulsification via solubilization measurements: T. J. Lin, Haruki Kurihara, and Hideaki Ohta. *Journal of the Society of Cosmetic Chemists* **28,** 457 (August 1977)

Synopsis—In the course of investigating the effects of surfactant location on O/W emulsification, it was discovered that there existed a useful correlation between the maximum amount of aqueous phase that could be solubilized in the oil phase containing the emulsifier and the average droplet size of the emulsion subsequently formed. Experiments were carried out with liquid hydrocarbons and many other oils frequently used in cosmetic emulsions. The emulsifiers used included various nonionic, anionic, cationic surfactants, and their mixtures. Analysis of the solubilization measurements and microphotographically obtained emulsion droplet size distribution data clearly indicated that the point of optimum O/W emulsification, i.e., the point where the finest O/W emulsion was formed in emulsifying with a series of surfactant mixture, corresponded to the point of maximum solubilization provided that the latter fell in a region where O/W emulsion formation was possible. In some systems studied, the maximum solubilization points were found in the region where only W/O emulsions could be formed under the experimental conditions. In such a case, the optimum O/W emulsions were generally found near the W/O–O/W transition point. The correlation held quite well in spite of the differences in the type and ionic nature of the surfactants employed.

Diffusion theory analysis of transepidermal water loss through occlusive films: Ira Weil and Henricus M. Princen. *Journal of the Society of Cosmetic Chemists* **28,** 481 (August 1977)

Synopsis—It is shown that simple diffusion theory dictates that the application of an occlusive film on skin always results in a decrease in transepidermal water loss (TWL), as expected intuitively. The basic inconsistency in a previous analysis, which seemed to predict the possibility of the opposite effect, is pointed out.

J. Soc. Cosmet. Chem., 28, 415–425 (August 1977)

The physical properties of fingernails
I. Apparatus for physical measurements

MICHAEL J. MALONEY and ELMER G. PAQUETTE *Bjorksten Research Laboratories Inc., P.O. Box 9444, Madison, WI 53715;* and ALBERT SHANSKY *Bettswood Road, Norwalk, CT 06851.*

Received September 30, 1976.

Synopsis

Miniature APPARATUS for measuring the PHYSICAL PROPERTIES of FINGERNAILS have been developed and tested. Included are a device for cutting test specimens; a template for preparing tensile bar samples; apparatus for performing flexural, tensile, and tearing tests; and a device for determining impact absorption. Whenever possible, methods were based on standard testing procedures so that recognized interpretative formulae could be used for analyzing experimental results. The range of physical properties found for the fingernails tested are as follows: flexural strength 4,928 to 17,653 psi; tensile strength 4,464 to 17,081 psi; tearing resistance 274.3 to 676.2 lb/in. and impact absorption (rebound ratio) 0.4632 to 0.7273.

INTRODUCTION

A number of investigators have reported on studies involving the human fingernail. While all of these studies have proved revealing, they have, as a group, suffered from one or more of the following limitations: (1) inadequate number of tests or subjects, (2) inadequate measuring techniques, (3) inadequate analysis or interpretation of results.

Bean (1) has meticulously studied the growth of his left thumbnail over a period of twenty-five years. His observations regarding the effect of age and a case of mumps are noteworthy and his philosophy amusing. Caputo and Dadati (2) and Jarrett and Spearman (3) have made significant contributions to the understanding of nail structure. Donsky (4) and Lazar (5) have sounded a warning note regarding the use of so-called nail hardeners. Dixon (6) attempted to evaluate the effect of a commercial nail food on nail splitting. While her results indicated no beneficial effect, she concluded that the trial was an educational success.

Michaelson and Huntsman (7) attempted to provide a numerical answer to the question of whether or not gelatin in the diet has an effect on nail hardness. They used a Knoop indentor to evaluate hardness, and while they concluded that gelatin increases hardness, the validity of their data has been questioned by Newman and Young (8). These latter authors have proposed that flexural measurements of fingernails should

provide the maximum information in the most direct manner (9). Baden (10) also studied nail flexibility and developed two additional methods for measuring modulus of elasticity.

Having independently arrived at the same conclusion as Baden, Newman, and Young, and having designed and built an apparatus for measuring flex strength, the authors support their conclusions regarding the value of flexural data. In addition, the authors have also devised apparatus and techniques for measuring tensile strength, impact absorption, and tearing strength of fingernails. Three of these properties are obtained by adapting a commercially available testing machine (the Instron tester). We consider this feature particularly important, since it allows other workers to perform comparable experiments. The fourth test (impact absorption) employs apparatus of our own design. However, the innate simplicity of the device insures that it could be easily duplicated by others.

Of the 4 tests, flexural strength and impact absorption have been demonstrated to be nondestructive. This feature allows the same nail to be tested several times and is invaluable for experiments, where it is desirable to determine the effect of exposure to various environments. Also, since each sample can serve as its own control, the number of experiments necessary to achieve statistical significance is greatly reduced.

The nail samples used for our studies were obtained from both living donors (large clippings) and cadavers. The donors ranged in age from 28 to 98 years and were about evenly divided between males and females.

DESCRIPTION OF THE APPARATUS

FLEXURAL TESTING APPARATUS

The procedure for determining flexural properties of plastics is described in ASTM method D-790 (11). The specifications call for a specimen, in the form of a rectangular bar, which is positioned on 2 supports and a load applied at the midpoint of the span.

The apparatus normally used for these tests is far too large to accommodate fingernails. To overcome this problem, therefore, a miniature fixture (Fig. 1), to be used in conjunction with an Instron tester was designed and fabricated. Even though the apparatus is much smaller than that normally used, the ratio of sample thickness to support radii is not changed, and the standard interpretive formulae may be employed.

SAMPLE CUTTING APPARATUS

In order to obtain reasonable accuracy when performing flexural tests, it is extremely important that the cut sides of the test specimens be as nearly parallel as possible. In our opinion, the method employed by Newman and Young (wherein the surfaces were sanded lightly) was not entirely satisfactory. Therefore, we have developed a device (shown in Fig. 2), which employs two rigidly mounted razor blades to accurately cut parallel samples for our tests.

In using the apparatus, a fingernail clipping is first conditioned by soaking it in distilled water. Then the clipping is flattened by clamping it between 2 sheets of clear plastic for at least 20 min. The flattened nail is carefully positioned on the cutting edges and

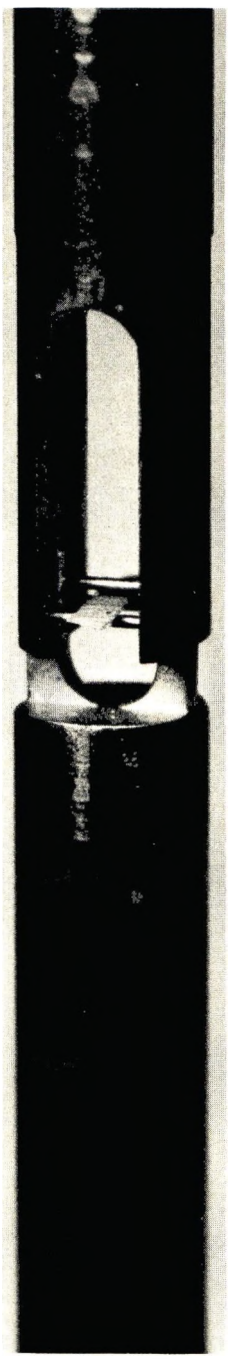

Figure 1. Apparatus for measuring the flexual properties of fingernails

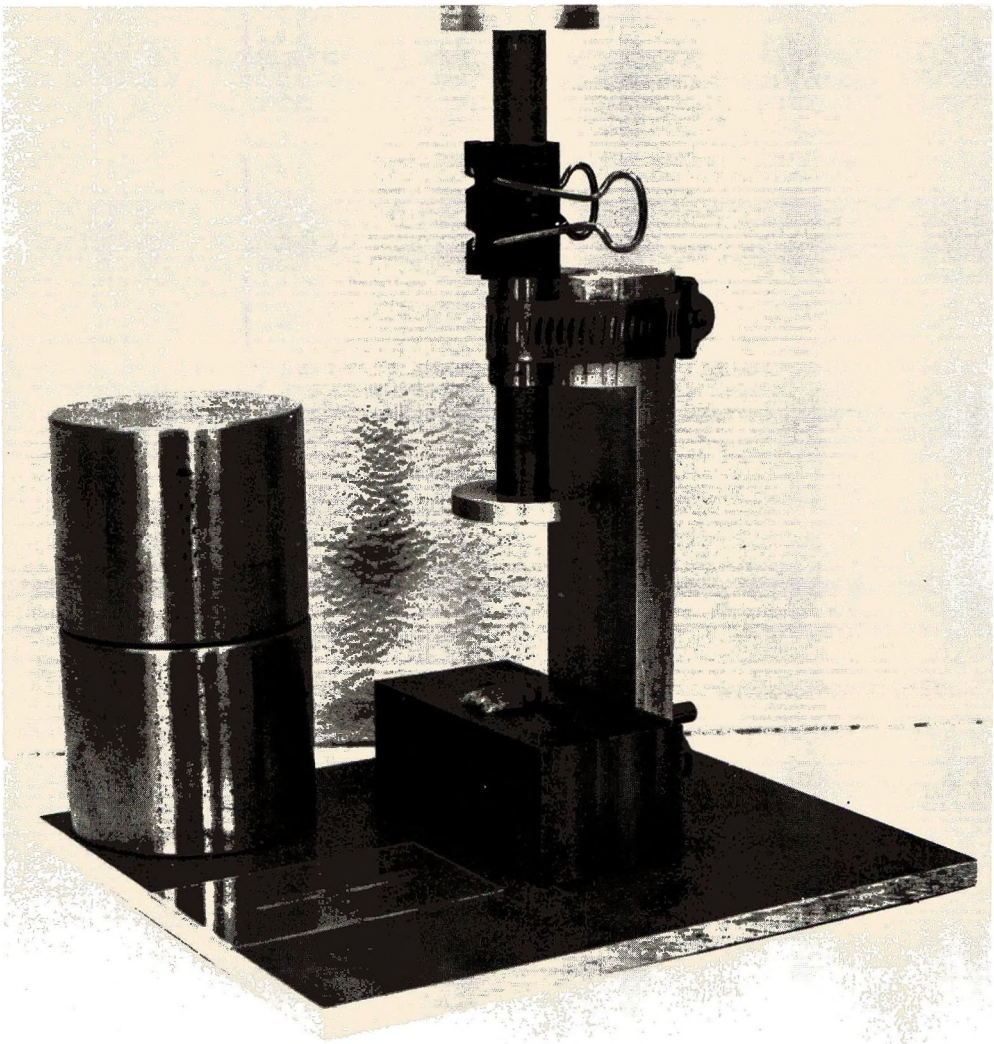

Figure 2. Apparatus for cutting fingernail test specimens

covered with a rigid plastic backing plate. A movable plunger is brought in contact with the plastic, and a weight is applied to the plunger. The weight forces the sample between the blades resulting in a clean sample, which is parallel to within a few hundred thousands of an inch. All of the specimens used for these experiments were conditioned to 25°C and 65 per cent RH before testing.

FLEXURAL TESTING EXPERIMENTS

As soon as a sufficient quantity of fingernail samples had been cut and conditioned initial experiments aimed at determining the capabilities of the apparatus were begun. During testing, the samples were subjected to a total deflection of 0.02 in. at a crosshead speed of 0.05 in./min. The testing machine is calibrated to measure forces in

the range of 0 to 2 lb and a strip chart recorder, driven at 10 in./min, provides a load/deflection curve. By combining low crosshead speed with a high rate of chart traverse, excellent resolution of stress–strain data are obtained. Also, since the samples are only slightly deflected during testing, no physical damage is done to the nails.

Initially, tangent modulus of elasticity, stress at a given strain, and flexural yield strength determinations were calculated for each sample. Ultimately, however, we determined that the flexural yield strength values were the most representative and thereafter only that value was determined. In our preliminary experiments with this apparatus, we tested a total of 92 different fingernail samples having a range of flexural yield strengths from 4,928 to 17,653 lb/in.^{2}

TENSILE TESTING APPARATUS

The procedure for determining the tensile properties of plastics is described in ASTM method D-638 (12). The specifications call for a specimen in the form of a rectangular bar having a reduced cross-section at the point where fracture is desired.

As with the flexural tester, the apparatus normally used for cutting the test specimens and performing the tests is far too large to accommodate fingernails. Once again, therefore, we designed and fabricated a series of miniature fixtures for sample preparation and testing.

TENSILE BAR FABRICATION

To obtain the reduced cross-section (dog bone) specimens necessary for this test we constructed the device shown in Fig. 3. The rectangular specimens are clamped in the template, and the necessary excess material removed by gently filing with a tool makers file. Since the samples are quite small, it is necessary to observe the work area through a low power microscope during the filing operation.

The resultant specimens are 0.032 in. wide in the reduced area and 0.100 in. wide in the area which is gripped in the tester. The 0.032 in. dimension was found to be crucial as samples having any larger cross-section were highly prone to jaw breaks.

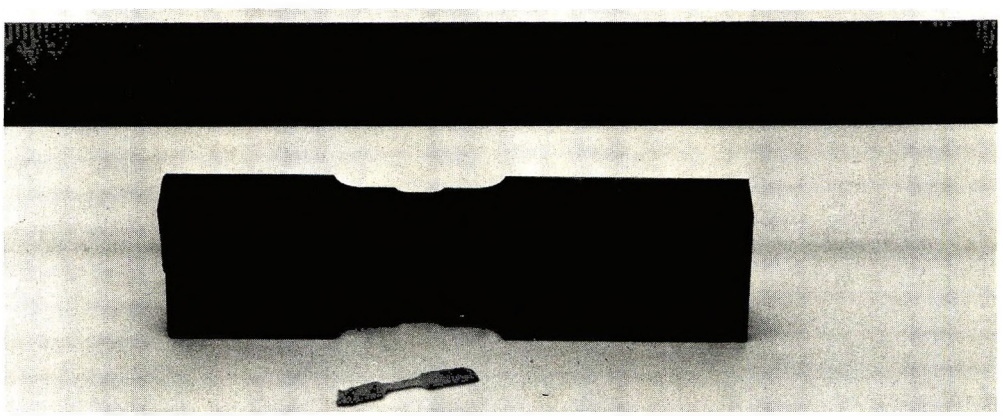

Figure 3. Template for preparing tensile samples from fingernails

TENSILE TESTING EXPERIMENTS

Our preliminary investigations indicated that the clamping mechanism would be the most important factor in both the tensile and tearing apparatus. We have found fingernails to be extremely plastic in nature. Therefore, when they are clamped between 2 flat surfaces, they almost immediately assume the new dimensions and slide from the clamp when a force is applied.

To alleviate this problem, it was necessary to construct a set of clamping jaws having directional serrated faces. The serrations act as miniature "teeth" and grip the nail securely without weakening it to such an extent that breakage takes place within the jaws.

Because of plastic deformation by the nails, it is necessary to insert shims to limit the penetration of the gripping "teeth." Each nail is measured, and then a shim selected which will limit the penetration to 0.005 in., since we have found that this is sufficient to insure a secure grip without propagating jaw breaks.

Figure 4 shows the apparatus performing a tensile test. All tests were conducted at a

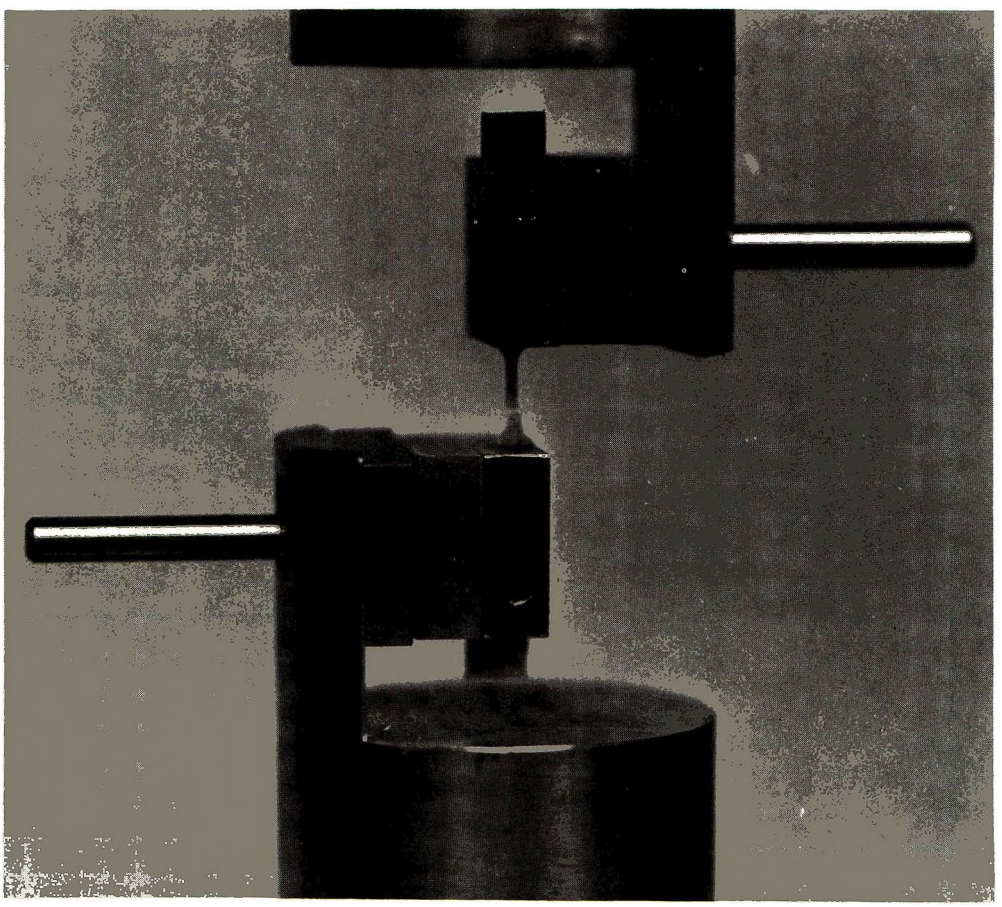

Figure 4. Apparatus for performing tensile tests on fingernails

crosshead speed of 0.2 in./min with the machine calibrated to measure forces in the range from 0 to 20 lb. In these initial tests, a total of 196 samples were tested. The tensile strength values determined from these samples ranged from 4,464 to 17,081 lb/in.^{2}

TEARING TEST APPARATUS

The objective of the tearing test is to simulate the action that occurs when a fingernail is torn. In order to gain a better understanding of the mechanisms involved, a "living" fingernail was torn *in situ,* and the results were carefully observed.

As a result of the *in situ* tearing experiment, we concluded that the action involved closely resembled that of a piece of paper being held in both hands and torn. Once the initial break has occurred, the stresses concentrate at the point of failure and propagate the tear along the path of least resistance.

In order to translate this action to a physical test, it was evident that the clamping jaws must be free to rotate so that the stresses could follow the line of the tear. This was achieved by attaching the jaws by means of a pin whose axis coincided with the edge of the nail where the tear would originate. Figure 5 shows the clamping jaws with 1 jaw open to reveal the clamping "teeth."

During the actual test, stress is applied to the edge of the nail until failure begins to occur. As the test proceeds, the jaws rotate concentrating the stress at the point where failure is occurring. Figure 6 shows the apparatus modified for tearing tests. The tests were conducted at a crosshead speed of 0.05 in./min with the machine calibrated to measure forces in the range from 0 to 20 lb.

TEARING TEST EXPERIMENTS

Specimens for the tearing experiments are prepared in the same way as those employed for the flexural strength test. In this case, however, there were no standard

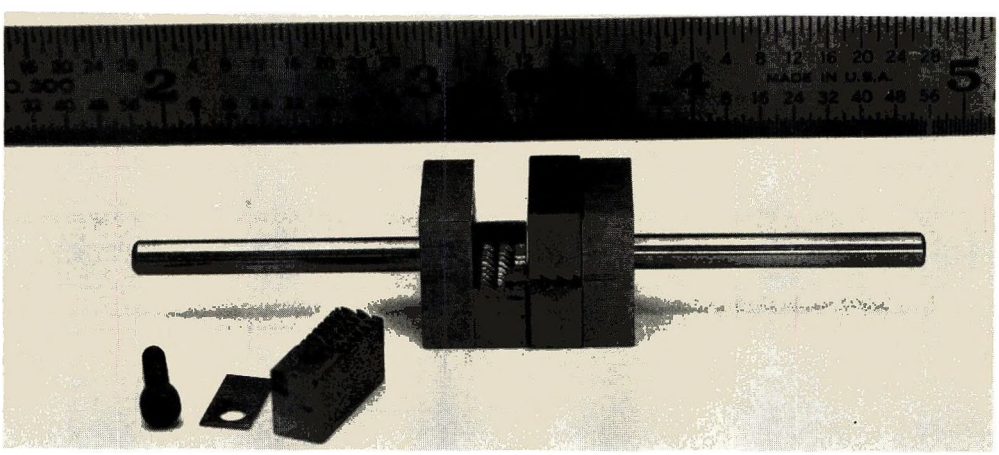

Figure 5. Clamping jaws used to secure tensile and tearing specimens for testing

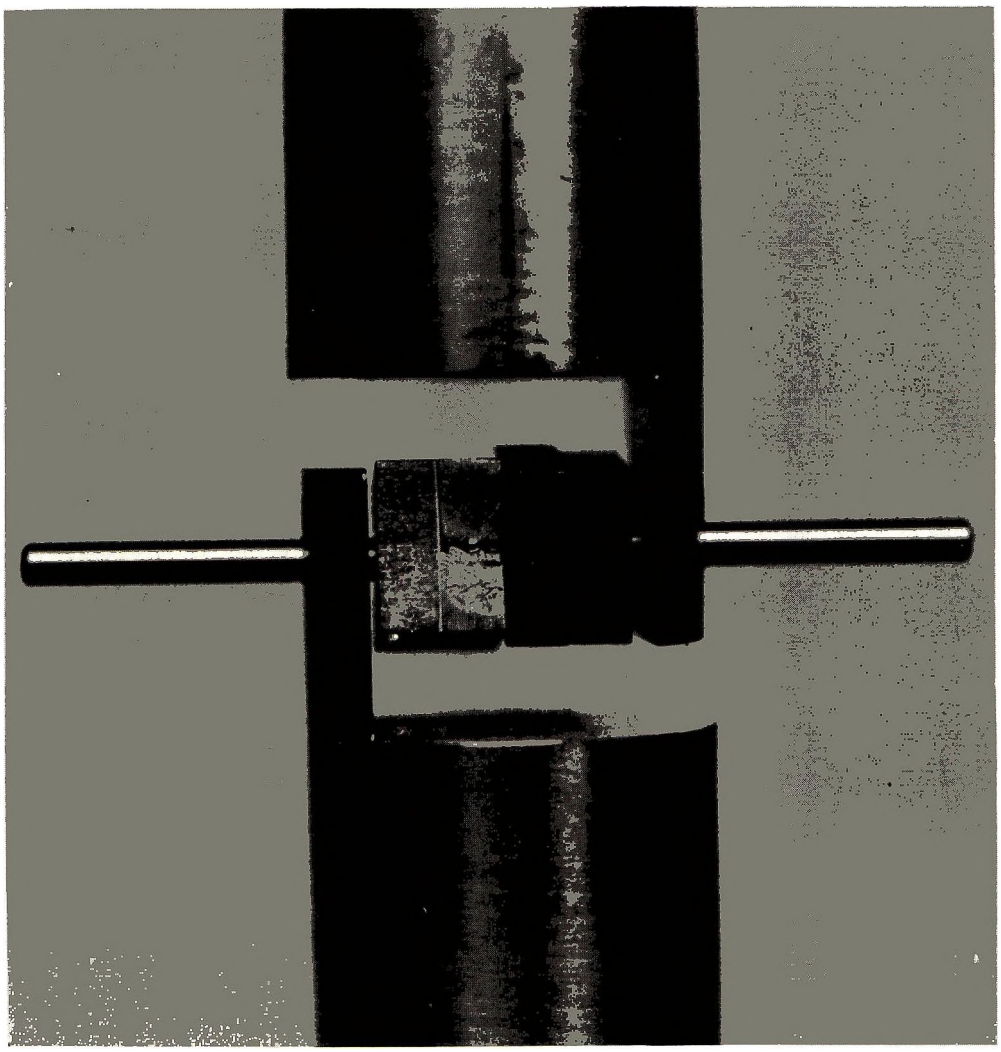

Figure 6. Apparatus for performing tearing tests on fingernails

methods to use as a guide, and we were forced to develop our own criteria for sample evaluation.

Before beginning the test, each fingernail specimen was carefully measured. The samples were then subjected to stress until failure occurred, and the force necessary was recorded. The results were plotted as tearing resistance in pounds per inch of nail thickness. A total of 15 fingernail samples were tested, and the values obtained ranged from 274.3 to 676.2 lb/in.

IMPACT ABSORPTION TESTER

The objective of the impact absorption test is to determine the effect of the impact of a swinging pendulum on a rigidly clamped sample. As with the previous tests, we found

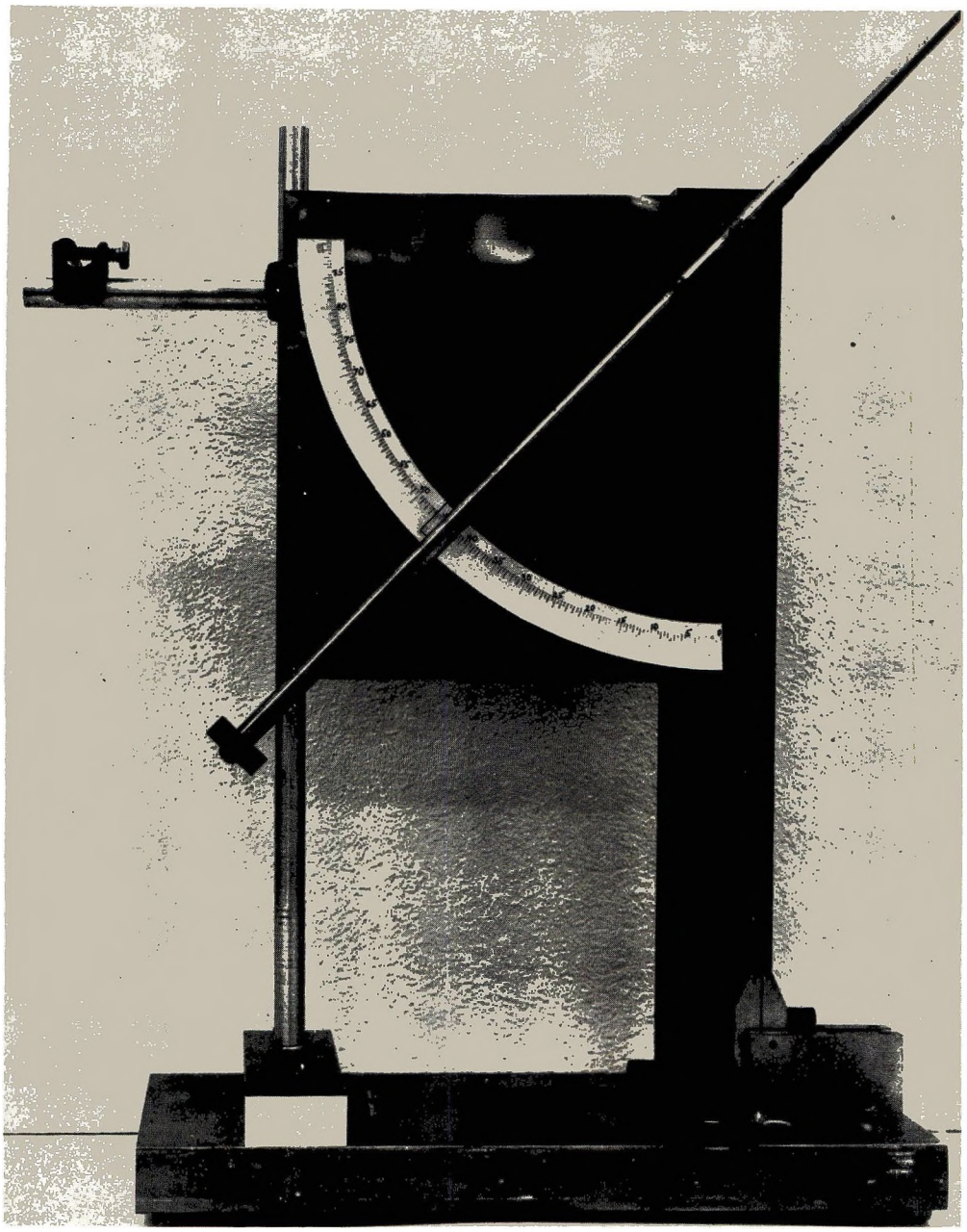

Figure 7. Apparatus for performing impact absorption experiments

that there was no suitable equipment available for testing samples of this size. Unlike the previous tests, however, this experiment could not be performed in the Instron or by modifying any other existing equipment. The simple apparatus which we have developed for this purpose is shown in Fig. 7.

IMPACT ABSORPTION EXPERIMENTS

The operation of the apparatus is as follows: a conditioned and inspected fingernail sample is placed in the clamp at the lower right hand side of the tester. The sample is clamped so that 1/8 in. of the nail protrudes from the top of the clamp. The pendulum, which has been resting in a horizontal position on the stop at the upper left side of the apparatus, is released and strikes the sample 1/16 in. above the clamp.

After striking the sample, the pendulum rebounds, and the rebound is observed and recorded. The pendulum continues to strike the sample, and the continually decreasing rebounds are observed and recorded. We have found it convenient to use a tape recorder to preserve the operator's observations, since it allows him to devote full attention to the mechanism.

The actual rebound in degrees is converted to rebound ratio by dividing the height in degrees of observed rebound by height in degrees of the starting point. For example, if the first rebound was observed to be 56.4 degrees, dividing by the starting point (90°) we would obtain a rebound ratio of 0.6267. If the second rebound was then observed to be 35.2 degrees, dividing by the starting point (56.9°), we would obtain a value of 0.6241.

The first 5 rebounds are converted in this manner, and the rebound ratios averaged, and the standard deviation determined. The procedure is repeated 3 times for each sample in order to reduce the chances of error due to an incorrect measurement and as a check against possible sample degradation due to the test itself.

In the experiments performed to date, a total of 64 different fingernail samples have been tested. The rebound ratio values obtained have ranged from 0.4632 to 0.7273.

SUMMARY

We have described 4 pieces of apparatus for measuring physical properties of fingernails. We have also presented a brief description of the operation of each apparatus and a range of experimental results which we have obtained from each. In our opinion, the tests provide a much needed addition to the state of the art in this area, and we hope that others will find them as useful as we have.

We regret that, due to space limitations, we could not include statistical interpretations of the results obtained. We are currently preparing another paper in which we intend to include this information. Also included will be data demonstrating differences in physical properties attributable to age and sex of the donor as well as hand and digit of nail origin.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Del Laboratories, Inc., who provided the financial support, which made this program possible, and to Patrick Harding who prepared the photographs of the apparatus.

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Society of Cosmetic Chemists Award Sponsored by International Flavors & Fragrances, Inc.

The Society of Cosmetic Chemists Award sponsored by International Flavors & Fragrances, Inc., was presented to Roger K. Curtis and Don R. Tyson of Redken Laboratories, Inc., for the most meritorious paper which was entitled "Birefringence: Polarization Microscopy as a Quantitative Technique of Human Hair Analysis."

Formal presentation of the Award was made by Dr. Karl Laden, Society of Cosmetic Chemists President, during the Awards Luncheon on May 5 at the Hotel Bonaventure in Montreal, Canada. The Award consists of an inscribed scroll and a $2,000 honorarium.

Left to right: Dr. Karl Laden, SCC President; Roger K. Curtis, Redken Laboratories, Inc., Awardee. Absent-Don R. Tyson, Redken Laboratories, Inc., Awardee

J. Soc. Cosmet. Chem., **28**, 427–439 (August 1977)

5-Brom-5-nitro-1,3-dioxan - ein neues Konservierungsmittel für die Kosmetik

PETER LORENZ*

Synopsis — 5-Brom-5-nitro-1,3-dioxan — A New Preservative for Cosmetics. — Bronidox®, a new preservative, is 5-bromo-5-nitro-1,3-dioxane. In concentrations of 0.02 to 0.05 % it is active against gram-positive and gram-negative bacteria as well as fungi. Toxicological and dermatological investigations demonstrate that the compound is tolerated without adverse reactions. Attempts to produce sensitization reactions failed. This compoud is currently recommended for the preservation of shampoos and foam baths.

1. Einleitung

Bei der Entwicklung und Produktion von Kosmetika hat das Problem der Konservierung einen hohen Stellenwert. Unter Konservierung versteht man normalerweise die Aufrechterhaltung eines gegebenen Zustandes. Dabei muß man beachten, daß der Zustand eines kosmetischen Erzeugnisses durch mancherlei Einflüsse beeinträchtigt werden kann. Zu erwähnen wären physikalisch-chemische Einflüsse wie Licht, Sauerstoff, Wärme und Verpackungsmaterial, Wirkungen von Enzymen, die durch Pflanzen- und Organextrakte eingebracht werden, und nicht zuletzt Einflüsse von Mikroorganismen, die durch Rohstoffe, den Herstellungsprozeß und den Verbraucher in das Kosmetikum gelangen können.

Durch mikrobiellen Befall kann die Ansehnlichkeit eines kosmetischen Präparates stark in Mitleidenschaft gezogen werden. Es kommt zu Verfärbungen, Geruch und pH-Wert werden verändert, sichtbarer Bewuchs tritt auf *(Bild 1)*, durch Konsistenzveränderung trennen sich die Phasen *(Bild 2)*, in klaren Produkten treten Flocken auf *(Bild 3)*, Emulsionen brechen, und durch Gasbildung kommt es zu Bombagen. Diesen äußeren, ästhetischen Merkmalen geht eine

* Fa. Henkel & Cie GmbH, Düsseldorf.

Bild 1

Bild 2

Bild 3

Beeinträchtigung der Wirksamkeit und eine Verminderung der Verträglichkeit des Kosmetikum parallel, so daß eine Konservierung gegen den mikrobiellen Verderb eine unabdingbare Forderung wird.

Im Sinne der eingangs gegebenen Definition von Konservierung als Aufrechterhaltung eines gegebenen Zustands käme für Kosmetika prinzipiell die Behandlung mit gespanntem Wasserdampf, das Tyndallisieren oder die Einwirkung von ionisierenden Strahlen in Frage. Auch die Sterilfiltration oder die Verwendung von Einmaldosis-Behältern wäre zu diskutieren, aber aus mancherlei Gründen, auf die hier nicht eingegangen werden soll, sind diese Methoden nicht praktikabel. Was bleibt, ist die Verwendung von mikrobistatisch bzw. mikrobicid wirkenden Substanzen, den sogenannten Konservierungsmitteln.

Bei der Auswahl des geeigneten Konservierungsmittels muß nun eine Reihe von Kriterien beachtet werden.

Für die Kontamination kosmetischer Präparate ist sowohl mit Pilzen — vorwiegend Penicillium-, Mucor- und Aspergillus-Arten — als auch mit Bakterien — überwiegend gramnegative Keime — zu rechnen (1). Bei der Bekämpfung dieser Keime zeigen jedoch die einzelnen Konservierungsmittel sehr unterschiedliche Wirkungsspektren. Bekannt ist beispielsweise bei den niedermolekularen p-Hydroxybenzoesäureestern sowie bei Germall 115® und Irgasan DP 300® eine Schwäche oder fehlende Wirkung gegen Hefen und andere Pilze (2). Andererseits kommt es häufig zu Inkompatibilitäten zwischen Antimikrobika und anderen kosmetischen Inhaltsstoffen. Auch der pH-Wert des zu konservierenden Produktes muß beachtet werden, da eine Reihe von Konservierungsmitteln nur einen begrenzten pH-Einsatzbereich hat.

In engem Zusammenhang damit steht die Stabilität des antimikrobiellen Wirkstoffs, die selbstverständlich in dem Kosmetikum gegeben sein muß.

Schließlich, und damit wird ein besonders wichtiger Gesichtspunkt angesprochen, muß auf eine gute physiologische Verträglichkeit des Produktes geachtet werden. Die Diskussionen um Hexachlorophen und quecksilberhaltige Konservierungsmittel nehmen einen breiten Raum in der Literatur ein (3), und Formaldehyd ist als Konservierungsmittel für Kosmetika beispielsweise in Japan verboten worden.

2. BRONIDOX®*, ein neues Konservierungsmittel

Die chemische Bezeichnung für Präp. B ist 5-Brom-5-nitro-1,3-dioxan. Das folgende Schema *(Bild 4)* verdeutlicht den Syntheseweg.

* E. W. der Fa. Henkel & Cie GmbH, im folgenden Präp. B genannt.

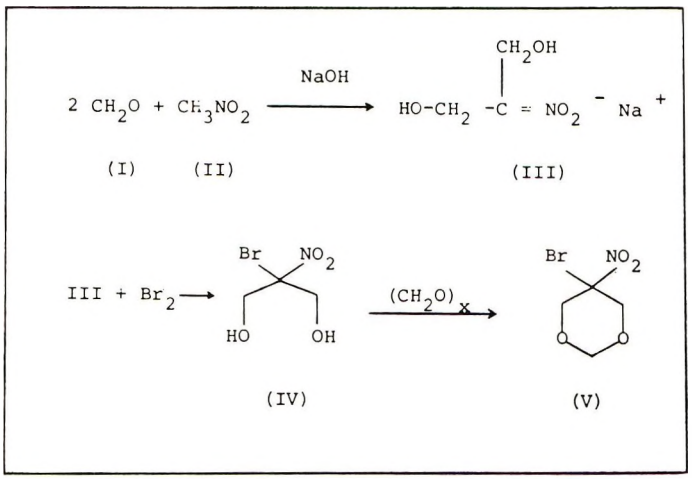

Bild 4

Synthese von 5-Brom-5-nitro-1,3-dioxan

Das Zwischenprodukt (IV) ist bereits 1919 von Schmidt und Wilkendorf (4) beschrieben worden und unter dem Markenzeichen Bronopol® (Boots Pure Drug Co. Ltd.) bekannt.

2.1 Physikalische und chemische Eigenschaften von Präp. B

Es ist ein fast farbloses kristallines Produkt. Seine physikalischen Konstanten sind in *Bild 5* zusammengestellt.

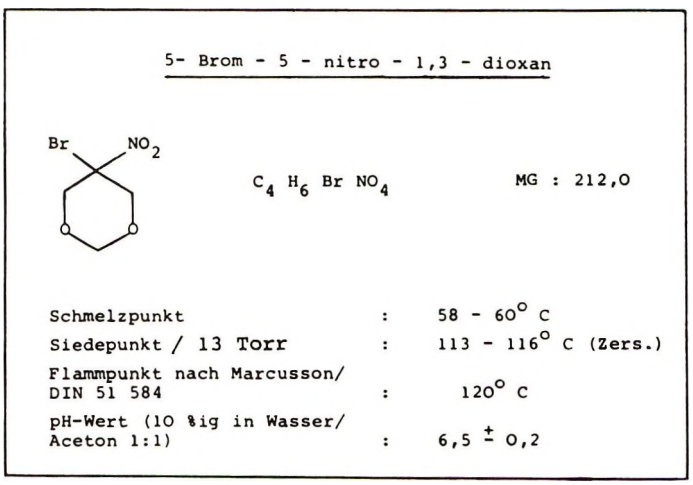

Bild 5

An Verunreinigungen enthält das Produkt < 0,2 % Natriumsulfat und einen Br-Anteil von < 0,3 % des Gesamt-Bromgehalts; es läßt sich anhand des Infrarotspektrums identifizieren, welches in *Bild 6* wiedergegeben ist.

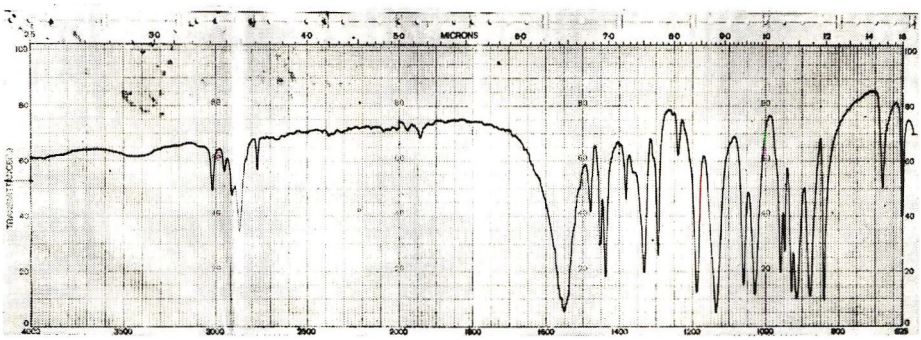

Bild 6
IR-Spektrum von 5-Brom-5-nitro-1,3-dioxan

Dünnschichtchromatographisch zeigt Präp. B auf Fertigplatten aus Kieselgel F 254 (E. Merck) einen R_F-Wert von 0,7, wenn man als Laufmittel Benzol/Chloroform/Isopropanol : 60/40/35 verwendet.

Ein wichtiges Kriterium für ein Konservierungsmittel ist seine Stabilität unter den Anwendungsbedingungen. Lösungen von 10 g in 60 g Äthanol und 30 g Wasser bzw. Pufferlösung wurden 10 Stunden auf 50° C erhitzt. Nach Abkühlung wurde mit Salpetersäure angesäuert und das abgespaltene Brom potentiometrisch titriert. Dabei ergaben sich zwischen pH 5 und 9 die im *Bild 7* wiedergegebenen Werte.

pH-Wert	Ionogenes Brom in % des Gesamt-Bromgehalts
5,2	0,63
7,0	0,63
9,0	0,96

Bild 7
Stabilität von 5-Brom-5-nitro-1,3-dioxan

Andere Lagertests über 17 Monate zeigten ebenfalls eine gute Stabilität zwischen pH 5 und 9. Auch die Lichtstabilität ist gut, was sowohl für die Substanz als auch in deren wäßrigen und nichtwäßrigen Lösungen gilt. Mehrwöchige Belichtungsversuche bei Raumtemperatur führten weder zu farblichen noch geruchlichen Veränderungen.

Mit mikrobiellem Verderb kosmetischer Produkte ist vor allem dann zu rechnen, wenn es sich um wasserhaltige Präparate handelt, denn Mikroben benötigen einen wäßrigen Lebensraum. Deshalb ist für die Wirksamkeit eines antimikrobiellen Mittels eine gewisse Wasserlöslichkeit zu fordern. Die Löslichkeit von Präp. B in Wasser bei 20° C beträgt 0,46 %. Dieser geringe Wert ist zweifellos von Nachteil, spielt aber keine allzu große Rolle, da Präp. B bereits bei einer Konzentration von 0,02 % seine antimikrobielle Wirkung voll entfaltet. Außerdem ist eine Lösung in 1,2-Propylenglykol auch kalt verarbeitbar. Eine allgemeine Übersicht der Löslichkeit in den gängigen Lösungsmitteln ist in *Bild 8* zusammengestellt.

Lösungsmittel	Temp. °C	Löslichkeit (g/100 g Lösungsmittel)
Wasser	20	0,46
	50	1,70
Äthanol	20	25
Isopropanol	20	10
1,2-Propylenglykol	20	10
Chloroform	20	50
pflanz. Öle	-	leicht löslich
Paraffinöl	-	unlöslich

Bild 8

Löslichkeit von 5-Brom-5-nitro-1,3-dioxan

2.2 *Antimikrobielle Eigenschaften von Präp. B*

Das zentrale Anliegen eines Konservierungsmittels ist sein Wirkungsspektrum gegenüber Mikroorganismen. Bei den zu bekämpfenden Mikroben handelt es sich sowohl um Bakterien als auch um Pilze. Viren können weitgehend aus dieser Betrachtung ausgeschlossen werden, da sie sich nicht in totem Material, also auch nicht in Kosmetika, vermehren können, sondern nur in Gegenwart lebender Organismen.

Von den Bakterien treten vorwiegend die sogenannten gramnegativen Arten auf, während die grampositiven Spezies für Kosmetika eine untergeordnete Rolle spielen. Aber gerade die gramnegativen Typen sind besonders schwer zu bekämpfen, und Mikrobiologen kennen den Keim pseudomonas aeruginosa als sogenannten Problemkeim.

Man muß also von einem Konservierungsmittel für Kosmetika erwarten, daß es gerade gegen gramnegative Organismen eine gute, zumindest ausreichende Wirkung hat. In *Bild 9* ist die Hemmwirkung von Präp. B gegen einige solcher Bakterien im Vergleich zu gängigen Konservierungsmitteln aufgeführt.

	Hemmwerte in ppm						
	5-Brom-5-nitro-1,3-dioxan	PHB-Äthylester	Chloracetamid	Hexachlorophen	Formaldehyd	Benzalkoniumchlorid	Phenylmercurinitrat
Escherichia coli	50	800	2500	500	62	20	0,3
Pseud. aeruginosa	50	800	2500	500	125	20	0,3
Proteus vulgaris	50	-	-	-	-	-	-
Aerobacter aerog.	50	-	-	-	-	-	-
Pseud. fluoresc.	50	-	-	-	-	-	-
Salmonella typhosa	50	-	-	-	-	-	-
Serratia marcescens	25	-	-	-	-	-	-

Bild 9
Hemmung gramnegativer Bakterien

Ein Vergleich dieser Werte zeigt, daß Präp. B eine hohe Aktivität gegen gramnegative Bakterien besitzt, was insbesondere auch für den „Problemkeim" pseudomonas aeruginosa gilt. Damit ist einerseits eine relativ sichere Beherrschung dieser Organismen gewährleistet, andererseits deuten die Zahlen bereits an, daß die Einsatzkonzentration im Vergleich zu anderen Konservierungsmitteln recht niedrig sein wird. An dieser Stelle sei auf die sehr niedrigen Hemmwerte von Benzalkoniumchlorid und Phenylquecksilbernitrat (siehe *Bild 9)* hingewiesen, auf die später noch näher eingegangen werden soll. Wenn auch grampositive Bakterien von untergeordneter Bedeutung für die Konservierung von Kosmetika sind, so soll doch in *Bild 10* ein Eindruck der Wirkung von Präp. B gegen diese Mikrobenklasse gegeben werden.

	Hemmwerte in ppm						
	5-Brom-5-nitro-1,3-dioxan	PHB-Äthylester	Chloracetamid	Hexachlorophen	Formaldehyd	Benzalkoniumchlorid	Phenylmercurinitrat
Staphylococcus aureus	75	500	2500	1-10	62	5	0,1
Staphylococcus albus	50	-	-	-	-	-	-
Mikrococcus varians	25	-	-	-	-	-	-
Streptococcus faecalis	75	-	-	-	-	-	-

Bild 10

Hemmung grampositiver Bakterien

Die Hemmwerte von Präp. B gegenüber grampositiven Keimen liegen in der gleichen Größenordnung wie die gegenüber gramnegativen Keimen. Das steht im Gegensatz zu zahlreichen anderen Antimikrobika, die gegenüber gramnegativen Bakterien deutlich weniger wirksam sind.

Betrachtet man schließlich die antimikrobielle Aktivität gegen Pilze, so stellt man fest, daß hier zahlreiche Konservierungsmittel Lücken in ihrem Wir-

	Hemmwerte in ppm				
	5-Brom-5-nitro-1,3-dioxan	PHB-Äthylester	Chloracetamid	Formaldehyd	Benzalkoniumchlorid
Candida albicans	25	800	1250	250	10
Saccharomyces cerevisiae	10	-	-	-	-
Aspergillus niger	10	250	1250	250	20
Mucor plumbeus	25	-	-	-	-
Penicillium camerunense	25	-	-	-	-
Fusarium species	10	-	-	-	-

Bild 11

Hemmung von Pilzen

kungsspektrum haben. Dies gilt nicht für Präp. B, dessen antimykotische Wirkung in *Bild 11* wiedergegeben ist.

Die Hemmwerte gegenüber Pilzen liegen in der gleichen Größenordnung wie die gegenüber Bakterien. Damit erweist sich diese Substanz als breit anwendbar, eine Lücke im Wirkungsspektrum tritt, im Gegensatz zu einigen anderen Konservierungsmitteln, nicht auf. Dies soll in *Bild 12* verdeutlicht werden, in welchem Auszüge aus einer Literaturzusammenstellung (2) wiedergegeben werden.

	durchschnittliche Hemmwerte in ppm		
	Staphylococcus aureus	gramnegative Bakterien	Pilze
5-Brom-5-nitro-1,3-dioxan	75	50	25
Benzylalkohol	25	2250	5000
Formaldehyd	62	100	250
Piorin	5	50	100
Osmaron	10	50	1000
Bronopol	50	25	125

Bild 12

Mit dem genannten Zahlenmaterial soll nicht der Eindruck erweckt werden, daß mit Präp. B jeder Keim beherrscht werden kann. Es sind auch bereits Mikroben bekannt, wie gewisse Norcardia-Typen, die den Actinomyceten zuzurechnen sind, bei denen Hemmwerte von 100 ppm gefunden werden. Ebenso ist nicht auszuschließen, daß es bei massiver Dauerbelastung, zum Beispiel bei mangelnder Betriebshygiene, zur Ausbildung resistenter Stämme kommen kann. Die bisher bekannten umfangreichen Ergebnisse, die hier nur auszugsweise wiedergegeben werden konnten, weisen Präp. B jedoch als Konservierungsmittel von großer Wirkungsbreite und hoher Aktivität aus.

An dieser Stelle ist eine kurze Bemerkung zum Mechanismus der antimikrobiellen Wirkung von Präp. B angebracht. Die Verbindung wirkt nicht als Formaldehydabspalter, etwa in Umkehrung der Synthese-Reaktion. Dies ist zum einen durch Stabilitätsprüfungen nachgewiesen, zum anderen sind die Hemmwerte gegenüber den meisten Keimen viel geringer als die von Formaldehyd.

Die derzeit wahrscheinlichste Erklärung der antimikrobiellen Wirkung von Präp. B beruht auf einer Oxidation der Thiolgruppen von Mercaptoaminosäuren. Stretton und Manson (5) deuten die Wirkung von α-Bromnitroverbindungen auf Mikroorganismen nach folgendem Schema *(Bild 13)*.

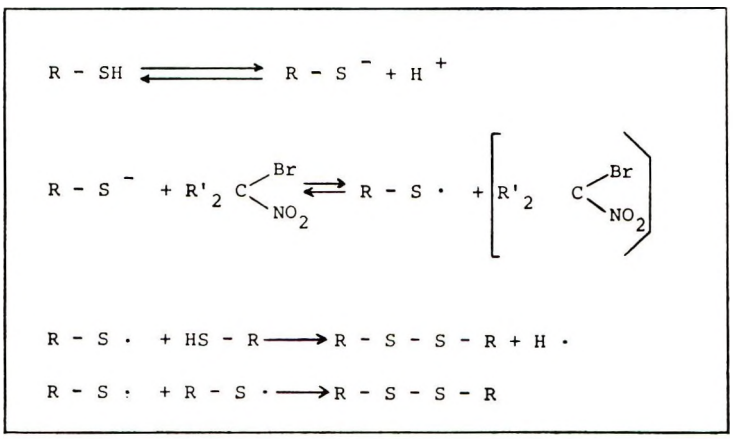

Bild 13
Reaktion von α-Bromnitroverbindungen mit Sulfohydrylgruppen

Demnach würde in einem reversiblen Schritt die Bromnitroverbindung von einem Thiolat-Anion ein Elektron übernehmen und das gebildete Schwefelradikal in einem irreversiblen Schritt zu einer Verbindung mit einer Disulfidbrücke reagieren. Diese Deutung wird auch von der Tatsache gestützt, daß als Enthemmungsreagens für Präp. B bei mikrobiologischen Experimenten Cystein Verwendung findet.

2.3 Präp. B als Konservierungsmittel in Kosmetika

Wenden wir uns nun der konservierenden Wirkung in Kosmetika unter Bedingungen der Praxis zu, so muß zunächst einmal festgestellt werden, daß für eine diesbezügliche Aussage nicht allein gute Hemmwerte gegen Mikroorganismen genügen. So ist bekannt, daß es zwischen Konservierungsmitteln und anderen kosmetischen Inhaltsstoffen zu Inkompatibilitäten kommen kann. PHB-Ester, Chlorbutanol, phenolische Verbindungen, quaternäre Ammoniumverbindungen und Phenylquecksilberverbindungen werden beispielsweise an Polyäthylenglykole oder an Carboxymethylcellulose mehr oder weniger stark gebunden und in ihrer Aktivität gehemmt. Die Wirkung kationischer Konservierungsmittel wird von Aniontensiden unterbunden, und nicht-

ionische Emulgatoren vermindern oder unterbinden die konservierenden Eigenschaften von PHB-Estern, Dehydracetsäure oder β-Phenyläthanol.

Eine Auskunft über die Eignung eines Konservierungsmittels in Kosmetika kann erst der Praxistest liefern. Das Konservierungsmittel wird in kosmetische Rezepturen eingebracht, die anschließend mit einem geeigneten Gemisch aus Testkeimen belastet werden. In diesem Gemisch kommen grampositive und gramnegative Bakterien ebenso vor wie Hefen und andere Pilze.

Präp. B hat sich bei solchen Tests in einer Fülle von kosmetischen Präparationen bewährt. Dabei wurden alle Arten von Emulgatoren, Tensiden und Ölkomponenten sowie Pflanzen- und Organextrakte verwendet, und es wurden keinerlei Inkompatibilitäten beobachtet. In allen Fällen wurde ein guter Konservierungserfolg erzielt, und auch bei erhöhten Temperaturen und längeren Lagerungszeiten veränderten sich die Kosmetika weder farblich noch geruchlich, noch hinsichtlich ihrer Konsistenz. Letzteres ist aufgrund der bereits beschriebenen Stabilität von Präp. B auch nicht zu erwarten.

Für den angegebenen Konservierungserfolg ist eine Konzentration von 0,02 bis 0,05 % erforderlich, also eine im Vergleich mit den meisten bekannten Konservierungsmitteln äußerst geringe Menge. Als besonders vorteilhaft erweist sich dabei die Verwendung einer 10%igen Lösung in 1,2-Propylenglykol, die bei ca. 40° C den kosmetischen Rezepturen zugegeben werden kann.

Im Hinblick auf die vielen Variationsmöglichkeiten in der Zusammensetzung von kosmetischen Erzeugnissen ist es empfehlenswert, im Einzelfall die zur Konservierung erforderliche Mindestkonzentration durch Vorversuche und entsprechende Lagerungs- und Belastungstests zu ermitteln.

Nach den vorstehenden Ausführungen erfüllt Präp. B die mikrobiologischen und anwendungstechnischen Bedingungen, die an ein modernes Konservierungsmittel für Kosmetika gestellt werden müssen. Von ausschlaggebender Bedeutung ist jedoch auch die physiologische Verträglichkeit kosmetischer Inhaltsstoffe, also auch und gerade von Konservierungsmitteln.

2.4 Toxikologisch-dermatologische Untersuchungen von Präp. B

Zur Klärung dieser Frage sind Experimente an Tieren und Menschen erforderlich, und die umfangreichen toxikologisch-dermatologischen Versuchsergebnisse sollen abschließend dargestellt werden.

Die akute Toxizität liegt bei 590 mg/kg Maus bzw. 455 mg/kg Ratte, jeweils durch orale Applikation ermittelt. Der entsprechende Wert für intraperitoneale Applikation an der Ratte liegt bei 31,5 mg/kg.

Zur Ermittlung der subakuten oralen Toxizität wurden SPF-Ratten einem 90-Tage-Test unterzogen. Als tägliche Dosierung wurden 10 mg, 50 mg und 100 mg gewählt. Wie bei solchen Experimenten üblich, wurde auch eine unbehandelte Kontrollgruppe beobachtet, und weder hinsichtlich des Körpergewichtes, des Blutbildes und der Harnzusammensetzung noch bei biochemischen Untersuchungen ergaben sich für die 10-mg- und 50-mg-Gruppe Abweichungen von der Kontrollgruppe.

Zur Ermittlung der lokalen Verträglichkeit wurde eine Hautverträglichkeitsprüfung mit wiederholter Benetzung nach Burckhardt (6) am Kaninchen und am Menschen durchgeführt. Bei einer 0,5%igen Anwendungskonzentration konnten keine negativen Befunde erhoben werden. Ebenfalls ohne Befund war der Patch-Test an Kaninchen und Mensch, wobei die Anwendungskonzentration 0,5 % und die Kontaktdauer 24 Stunden betrugen.

Die Hautverträglichkeit wurde auch am Testmodell der haarlosen Maus geprüft. Dazu wurde das Produkt 1%ig 14 Tage lang täglich einmal auf den Rücken der Tiere gebracht, ohne daß es zu irgendwelchen Reaktionen kam. Dieselbe Prozedur wurde mit 5%iger Lösung ebenfalls reaktionslos vertragen.

Versuche zur Sensibilisierung am Meerschweinchen mit Hilfe des Freund'schen Adjuvans verliefen ohne negativen Befund. Auch bei Sensibilisierungsversuchen am Menschen erwies sich Präp. B als harmlos.

Schließlich wurde unter Aufsicht eines Dermatologen ein umfangreicher Gebrauchstest an einem großen Personenkollektiv durchgeführt, wobei mit Präp. B konservierte Shampoos und Schaumbäder zur Anwendung gelangten. Nachdem auch dieser Test mit gutem Erfolg abgeschlossen wurde, kann festgestellt werden, daß — bei sachgerechter Anwendung — das toxikologische Risiko gering ist.

Unter sachgerechter Anwendung ist gegenwärtig zu verstehen, daß das Produkt vom Hersteller für die Konservierung von Shampoos und Schaumbadpräparaten empfohlen wird. Speziell für diese Einsatzgebiete liegen umfangreiche Verträglichkeitsprüfungen vor.

Zusammenfassung

5-Brom-5-nitro-1,3-dioxan ist ein neues Konservierungsmittel, das in Konzentrationen von 0,02 bis 0,05 % sowohl gegen grampositive als auch gramnegative Keime und Pilze wirksam ist. Toxikologisch-dermatologische Untersuchungen erweisen die reaktionslose Verträglichkeit. Versuche zur Sensibilisierung ergeben negative Befunde. Das Produkt wird gegenwärtig zur Konservierung von Shampoos und Schaumbädern empfohlen.

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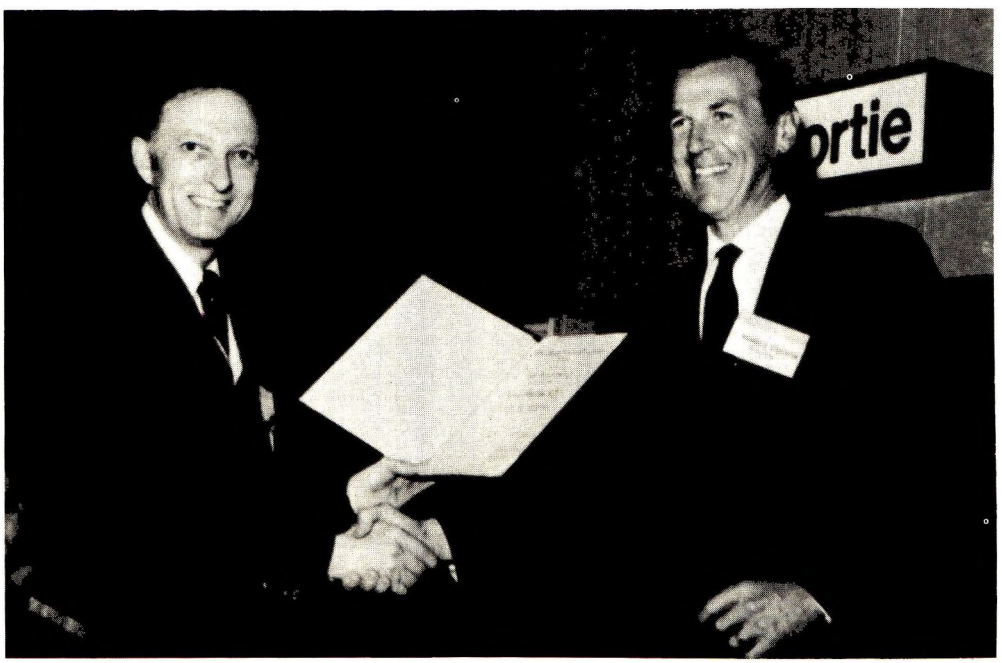
Society of Cosmetic Chemists Award Sponsored by Shaw Mudge and Company

The Society of Cosmetic Chemists Award sponsored by Shaw Mudge and Company was presented to Richard Stoughton, M.D., for his work in developing methods to study absorption of topical agents in man and animals.

Formal presentation of the Award was made by Dr. Karl Laden, President of the Society of Cosmetic Chemists, at the Awards Luncheon held May 5 at the Hotel Bonaventure in Montreal, Canada. The Award consists of a $2,000 honorarium and an inscribed scroll.



Left to right: Dr. Karl Laden, SCC President; Dr. Richard Stoughton, Scripps Clinic, Awardee

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Antiperspirant efficacy

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Synopsis

ANTIPERSPIRANT EFFICACY of ALUMINUM CHLOROHYDRATE "TYPE" INGREDIENTS is discussed. The optimal efficacy for aluminum chlorohydrate and aluminum bromohydrate in aqueous solution occurs at concentrations of 15 per cent (3.75 per cent Al) and 24 per cent (5.0 per cent Al), respectively. No difference in efficacy between aluminum chlorohydrate-$AlCl_3$ combinations and aluminum chlorohydrate alone, is found. Efficacy differences are observed as a function of vehicle. For example, aqueous formulations appear to be more efficacious than anhydrous formulations. Efficacy of aluminum-zirconium compounds is discussed in terms of variation of Al:Zr ratio. No differences are found.

INTRODUCTION

Antiperspirants as topical drugs have come under the scrutiny of FDA-OTC panels. Because of this interest and since the definition of antiperspirants is based on their efficacy, a study of the effectiveness of commonly used active ingredients would be useful. Unfortunately, there is a paucity of published information in this area. Recent papers have dealt with experimental designs and statistical interpretation of data (1,2, 3), mostly on formulated products. Since efficacy can be influenced by adjuvants in formulations, we believed an investigation of active ingredients in simple aqueous and nonaqueous vehicles worthwhile. In recognition of this information gap, we have studied the relationship between active ingredient efficacy with both concentration and solvent variations. We hope that this data will enlarge the cosmetic chemist's horizons, in developing new and improved vehicles for the application of a chosen antiperspirant.

To render this study both feasible and meaningful, we limited our investigational efforts to aluminum chlorohydrate "types" as well as aluminum-zirconium complexes.

Aluminum chlorhydrate, a 5/6 basic aluminum "salt," $Al_2(OH)_5Cl$, has been used as an antiperspirant for over 30 years (4). Other aluminum salts, such as aluminum chloride, were available as antiperspirants in the early part of the twentieth century, primarily for use by actors and models. The drawback of this product is its high acidity resulting in fabric damage and skin irritation. To circumvent this problem, buffers such as urea were used. Then in the early 1940s an internally buffered product, aluminum chlorohydrate, became available. In recent years, however, aluminum chloride has regained popularity, primarily when used in conjunction with basic aluminum "salts." In a twist of fate, aluminum chlorohydrate, which originally replaced buffered aluminum chloride systems, is now being used to buffer aluminum chloride, the dif-

ference being that, in the latter case, 2 active ingredients are used rather than one. Some products which use 2 active ingredients also use a buffer such as urea, amino acid, or an inorganic salt to decrease acidity. Other multi-active systems consisting of aluminum and zirconium salts have also received considerable attention in recent years. The effectiveness of all these products is of critical importance to cosmetic chemists.

We will discuss the efficacy of many of these systems and some of their isologs in relation to the effects of concentration and vehicle. For example, one may reasonably ask, "Is the efficacy of aluminum chlorohydrate in aqueous formulations as effective as hydroalcoholic or anhydrous formulations?" We will try to answer questions of this type, but first, a brief review of the clinical procedure will be described.

EXPERIMENTAL

DATA COLLECTION*

The efficacy data were obtained using 0.5 ml applications. A gravimetric method was employed to obtain these data (1). Panelists were required to abstain from the use of all antiperspirant materials from enrollment until completion of test.

Sweating of test panelists is induced by having the panelists sit in a room maintained at 100 ± 2°F and at a relative humidity of 35 per cent. Before collection of perspiration, there is an appropriate warmup period. All data were obtained 22 h after final application of product.

DATA TREATMENT

The geometric mean was used to calculate efficacy (2,3). In the statistical analysis, we use logarithmically transformed milligram weights. The per cent reduction is calculated as follows:

$$\text{Per cent Sweat Reduction} = [1\text{-antilog}\,(T' - C')] \times 100$$

where T′ and C′ are the average values of the logarithmically transformed milligram weights for the test (treated) and control (untreated) axillae.

RESULTS AND DISCUSSIONS

ONE-INGREDIENT FORMULATIONS

Dose response curves are normally available for drugs. Little information is available, however, on the variation of efficacy (response) with concentration (dose) for antiperspirants, when employed as topical drugs. Efficacy data for one of the more popular

*Efficacy data obtained from Hill Top Research, Inc., Miamiville, OH. For a detailed account of their method, see (1).

antiperspirant ingredients, aluminum chlorohydrate,* at 3 different concentrations, 10, 15, and 20 per cent w/w, are summarized in Table I. These efficacy values were obtained from different test panels. Average point estimates were obtained by taking antilogarithms of the average of the logarithms at each concentration. Analysis of variance on logarithmically transformed data, in conjunction with a Neuman–Keuls range test, shows the following order of effectiveness at 95 per cent confidence limits: 15 per cent > 20 per cent, and 10 per cent. No significant statistical difference in efficacy is observed between 10 and 20 per cent concentrations. Surprisingly, the efficacy reaches a maximum, rather than a plateau. Reasons for this occurrence are unknown. We have, however, observed similar trends with other basic aluminum "salts."

Table I
Per Cent Sweat Reduction for Aluminum Chlorohydrate[a]

	Concentration		
	10 Per Cent w/w	15 Per Cent w/w	20 Per Cent w/w
	25[b]	63	38
	(11–38)[c]	(57–68)	(30–47)
	38	56	35
	(27–48)	(43–69)	(23–46)
	36	58	50
	(26–47)	(50–67)	(39–60)
	43		44
	(30–55)		(38–51)
	40		37
	(30–49)		(26–47)
	51		
	(35–56)		
	46		
	(39–53)		
Average	39[d]	59	40

[a]Chlorhydrol.®
[b]Point estimate per cent sweat inhibition.
[c]Per cent confidence limits.
[d]Antilogarithm of average logarithms at each concentration.

Table II
Per Cent Sweat Reduction for Aluminum Bromohydrate[a]

Concentration Per Cent w/w	Per Cent Sweat Reduction	95 Per Cent Confidence Limits
10	52	43–61
24	63	60–66
28	51	46–56
36	46	38–54
43	46	39–53

[a]B.A.B.®

*In our studies, we used Chlorhydrol®, a product of Reheis Chemical Company, Division of Armour Pharmaceutical Company, Berkeley Heights, NJ 07922.

For example, an isolog of aluminum chlorohydrate is aluminum bromohydrate.* Efficacy data for this product are shown in Table II. Again, we observe a peaking effect. In this case, however, the maximum efficacy occurs at 24 per cent (5 per cent Al), whereas for aluminum chlorohydrate the maximum efficacy occurs at 15 per cent (3.75 per cent Al).

While the analysis shows a maximum for dose-response data, we are not totally convinced that this peaking effect is real. To help resolve this problem, we plan to run multiple crossover studies with aluminum chlorohydrate at several different concentrations.

ALCOHOL SOLUBLE ANTIPERSPIRANTS

Since many new products on the market use anhydrous or hydroalcoholic vehicles rather than predominantly aqueous ones, we explored the effect of solvent on antiperspirant activity.

Most nonaqueous formulations use an aluminum chlorohydrate "type" complex alone or in conjunction with $AlCl_3$. Since we already know the efficacy of aluminum chlorohydrate in aqueous systems at different concentrations (Table I), it would be instructive to compare the effectiveness of one of these systems with an analogous hydroalcoholic formulation. Table III shows the per cent sweat inhibition for a 50 per cent ethanol solution of aluminum chlorohydrate at 20 per cent to be 41 per cent. The alcohol has not attenuated the activity of this product, as can be seen by comparing the above efficacy with that in Table I (39 per cent) for the same product at an identical concentration. We have observed similar results for Al-Zr combinations. While hydroalcoholic systems are as efficacious as aqueous systems in the formulations studied, some reduction in activity for anhydrous systems has been noted.

Table III
Per Cent Sweat Reduction for Alcohol Soluble Antiperspirants

Antiperspirant[a]	Per Cent Sweat Reduction	95 Per Cent Confidence Limits
Aluminum chlorohydrate[b] propylene glycol complex	21	9-31
Alcohol soluble[c] aluminum chlorohydrate	47	40-55
Aluminum chlorohydrate[d]	41	31-52

[a]All solutions made up to 5 per cent Al in SDA-39C.
[b]Rehydrol®, Reheis Chemical Company, Division of Armour Pharmaceutical Company, Berkeley Heights, N.J. 07922.
[c]A.S.C.®, Reheis Chemical Company, Division of Armour Pharmaceutical Company, Berkeley Heights, N.J. 07922.
[d]50 per cent hydroalcoholic solution.

*B.A.B.®, Reheis Chemical Company, Division of Armour Pharmaceutical Company, Berkeley Heights, NJ 07922.

Two different type alcohol soluble products, which are applicable for anhydrous systems, are aluminum chlorohydrate-propylene glycol complex (A) and alcohol soluble aluminum chlorohydrate (B). Table III shows per cent sweat reduction values for these 2 materials at identical aluminum concentrations. The efficacy of B is greater than A. The difference in results may be a function of the water content of the active ingredient and, hence, the ethanol-water balance of the formulation. For example, the 20 per cent alcoholic aluminum chlorohydrate system contains *ca.* 4 per cent water, whereas the 25 per cent aluminum chlorohydrate-propylene glycol complex system contains a maximum 1 per cent water. It is possible that small amounts of water are necessary to catalyze antiperspirant activity of the metal salt. We plan to study thoroughly the relationship, if any, that exists between ethanol:water ratios and efficacy for a variety of alcohol soluble antiperspirants.

MULTI-INGREDIENT FORMULATIONS

In the evolution of antiperspirant formulation technology, combination systems of 2 or more active ingredients have recently generated much interest.

Today, many cosmetic chemists prefer 2 active ingredients in their formulation instead of one component systems. For example, many formulators use aluminum chlorohydrate-$AlCl_3$ combinations. One reason for interest in these systems is the belief that more acidic products (e.g., aluminum chlorohydrate + $AlCl_3$) have superior efficacy. There are hypotheses which correlate efficacy with pH. For example, the interaction of aluminum salts with skin protein is a function of pH (5). This type of reaction has been proposed as a possible mechanism for antiperspirant activity.

Table IV.
Per Cent Sweat Reduction for Aluminum Chloro- and Bromohydrate-AlC_3 Combinations

Concentration	Al:Cl Ratio		Al:Br Ratio	
Per Cent w/w	1:1	2:1	1:1	2:1
10	35[a] (23–48)[b]	44 (33–56)	52 (41–62)	52 (53–63)
20	49 (38–59)	38 (27–48)	—	—

[a]Point estimate per cent sweat inhibition.
[b]95 per cent confidence limits.

Table V
Per Cent Sweat Reduction for Al-Zr Complexes at Different Ratios

Al:Zr Ratio[a]	Per Cent Sweat Reduction[b]
0.5:1	45–<u>54</u>–66
2.0:1	50–<u>58</u>–68
4.0:1	48–<u>59</u>–70
6.0:1	50–<u>60</u>–69

[a]All at 10 per cent w/w.
[b]Point estimate underlined. Outer points at 95 per cent confidence limits.

For example, the maximum reaction of aluminum chloride with skin protein occurs at a pH of 3.51, with the binding of aluminum falling off sharply on either side of the pH. At low pH levels, skin protein exhibits a decreased activity for aluminum ions due to the existence of its carboxyl groups predominantly as the undissociated —COOH species. At high pH levels, the carboxyl groups are ionized to the $-COO^-$ state. Consequently, their interaction with aluminum would be expected to be enhanced. In light of the foregoing, it seems reasonable that sweat reduction mediated via the use of antiperspirants could be a function of pH, assuming that the mechanism of such activity is controlled by the precipitation of skin protein with the basic aluminum species.

Table IV compares efficacy results for aluminum chloro- and bromohydrate "types" with Al:halide ratios of 2:1 and 1:1. No significant difference between these lower and higher ratio products is evident for these aqueous formulations. It is, of course, possible that the more acidic species are skin irritants and, therefore, act antagonistically (i.e., as "properspirants"), thereby attenuating the properties of the aluminum complex.

In the search for new and effective antiperspirants, aluminum-zirconium combinations have aroused interest. We will only be concerned with nonaerosol aqueous formulations. Table V lists the efficacy for Al-Zr products, with Al:Zr ratios varying from 0.5:1 to 6:1. No significant differences in efficacy from product to product are evident. In general, it appears as if the effectiveness of these systems is comparable with 15 per cent aluminum chlorohydrate. It is believed, however, that these Al-Zr systems, once formulated, retain a higher proportion of their activity than aluminum systems; that is to say, their effectiveness appears less influenced by the chemical environment represented by the formulation medium.

SUMMARY

To summarize, we believe that, based on our data, the efficacy of some antiperspirant materials peaks at a particular concentration rather than reaching a plateau. Reasons for this effect are unknown. Vehicle also plays a role in controlling efficacy. For example, anhydrous systems have a lower efficacy than aqueous or hydroalcoholic formulations. Our data regarding the relationship between efficacy and vehicle are limited. We plan to fill in this gap, in the near future, by studying the relationship between ingredient efficacy and vehicle as well as variations in Al:Cl ratio and concentration. Finally, we have found that the efficacy of aluminum-zirconium complexes is independent of Al:Zr ratio.

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'J. Soc. Cosmet. Chem., 28, 447–455 (August 1977)

Studies on the molecular weight distribution of cosmetic protein hydrolysates

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Synopsis

MOLECULAR WEIGHT has been thought to be an important feature of COSMETIC GRADE PROTEINS and to be a critical factor affecting PROTEIN SUBSTANTIVITY to HAIR. The study reported in this paper was undertaken to show the relationship of molecular weight to protein substantivity. Using gel filtration and ultracentrifugation data were obtained that indicate peptides in the range of molecular weight 1000 are more substantive than the very high molecular weight molecules.

INTRODUCTION

Cosmetic grade protein hydrolysates are complex mixtures of various molecular weight polypeptides. Only approximate number average molecular weights have been previously reported. This study was undertaken to provide additional information about the distribution of molecular weights of collagen hydrolyzed by several methods, and to show if there is a relationship between molecular size and hair substantivity.

Two techniques were used for investigating the molecular weight distribution of cosmetic grade protein hydrolysates, gel filtration and ultracentrifugation.

Gel filtration is an established chromatographic method for the separation of molecules according to their size. The use of Sephadex®*, a bead-formed dextran gel, for gel filtration was introduced in 1959, and since has become a well-established method for fractionation and separation of molecules according to their size. Sephadex is cross-

*Sephadex®, Pharmacia Fine Chemical Inc., 800 Centennial Avenue, Piscataway, NJ.

linked dextran; the degree of crosslinking determines the molecular weight fractionation range.

Sephadex Type	Fractionation Range (Molecular Weight)	
	Peptides	Dextrans
G-10	– 700	– 700
G-15	– 1,500	– 1,500
G-25	1,000– 5,000	100– 5,000
G-75	3,000– 70,000	1,000– 50,000
G-200	5,000–800,000	1,000–200,000

Molecules of molecular weight above the upper limit of the ranges shown in the above chart are totally excluded from the gel. Molecules of molecular weight below these ranges are eluted from the Sephadex column in the above chart at a volume about equal to the total bed volume. Molecules between the upper and lower limits are eluted from the Sephadex column in a specific relationship to the molecular weight. Over a considerable range, the elution volume is approximately a linear function of the logarithm of the molecular weight.

The other method of determining molecular weight is by ultracentrifugation. The ultracentrifuge produces high centrifugal forces in order to measure the movement or redistribution of sedimenting particles. The distribution of the particles is observed by an interference pattern. From this interference pattern, a molecular weight or molecular weight range can be calculated.

In work with the ultracentrifuge, the material under investigation is placed in the centerpiece of the cell assembly. This cell assembly is constructed in a manner that permits light rays to pass through its entire length. After the cell is assembled and placed in a rotor hole, the rotor is then installed in the rotor chamber; the chamber is evacuated; and the rotor accelerates. The sample material is subjected to high centrifugal forces that causes the molecular particles to sediment. As the particles are redistributed, the light from the optical system light source can be transmitted through the rotating cell. By means of this light, the optical elements translate particle movement into an optical pattern, from which molecular weight can be calculated.

METHODS AND MATERIAL

MATERIALS

Protein Hydrolysates

1. Collagen hydrolyzed with papain to a formol nitrogen of 10.0*
2. Collagen hydrolyzed with steam to a formol nitrogen of 6.0*
3. Collagen hydrolyzed with acid to a formol nitrogen of 10.0*

*Inolex Corporation, Chicago, IL.

Sephadex Gels

Sephadex G-10
G-15
G-25
G-75
G-200

METHODS

Gel Filtration

Cosmetic grade protein hydrolysates were thought to have average molecular weights of between 1,000 and 10,000. With this range, Sephadex G-15 or G-25 would be the gel of choice for the separation of these peptide molecules. Chromatographic columns were prepared by packing 1.5 × 100 cm columns with gel previously swollen in 0.25 *M* NaCl. These columns were equilibrated with the saline. Protein hydrolysate samples were dissolved in the equilibration solution at a concentration of 180 mg/ml, and 3 ml of this solution was applied to the top of the column. The material was eluted at the rate of 0.25 ml/min. The presence of polypeptides was detected by measuring the absorbance at 280 nm using a continuous flow spectrophotometer. The curves generated showed that all of the sample was eluted in the void volume (above in the upper exclusion limit) from the Sephadex G-15 column, and some of the sample was eluted in the void volume from the Sephadex G-25 column. These gels, therefore, were not the appropriate ones for the separation of the cosmetic grade protein hydrolysates being investigated.

After the initial chromatographic runs were completed, Sephadex G-75 and G-200 columns were packed in the same manner as the G-15 and G-25 columns. From the absorbance graphs of these runs, it was determined that G-75 was the most useful in determining the molecular weight distribution of the hydrolysates being studied.

The 3 commercially available cosmetic grade proteins described above were studied using the Sephadex G-75 column. The peptides were eluted with 0.25 *M* NaCl at a rate of 0.15 ml/min and detected with absorbance measurements at 280 nm.

To determine the molecular weight relationship to elution volume, the Sephadex G-75 column was calibrated. First, the void volume was determined by eluting Blue Dextran; the elution volume is equal to the void volume. The total volume was calculated from the geometry of the column. A calibration curve was generated by eluting proteins of known molecular weights from the same Sephadex G-75 column and under the same conditions used in the experimental run.

Protein	Molecular Weight
Aldolase	158,000
Ovalbumin	45,000
Chymotrypsinogen	25,000
Ribonuclease A	13,700

The elution volumes of the proteins shown in the above chart were plotted against the logarithm of the molecular weight.

PROTEIN SUBSTANTIVITY OF MOLECULAR WEIGHT FRACTIONS

Evaluation of the 3 unfractionated cosmetic grade proteins on hair showed that the enzyme digested hydrolysate was the most substantive. For this reason, it was selected as the protein for study of the substantivity properties of its various fractions. A large G-75 Sephadex column (5.0 × 100 cm) was used, since much greater quantities of material than could be obtained from the small column were required to conduct the substantivity measurements on the various fractions.

The sample of the enzyme hydrolyzed material, 50 ml of an 18 per cent solution in 0.25 *M* NaCl, was applied to the bottom of the column and eluted at a rate of 0.5 ml/min. After 4 h, the column was inverted and the flow allowed to proceed as a descending chromatograph. This procedure insures a straight horizontal front.

Fractions were collected every 15 min. These fractions were then pooled into 4 main fractions: (1) greater than molecular weight 30,000; (2) 30,000–5,000; (3) 5,000–1,000; and (4) less than 1,000. It was necessary to desalt each of the fractions, because each was dissolved in 0.25 *M* NaCl. Desalting was accomplished on a Sephadex G-10 column. Each of the fractions was first freeze-dried, redissolved in 10 ml of water, applied to the column, and eluted with water. The solid material was used to prepare 5 per cent solutions of each fraction.

The relationship of molecular weight to substantivity to bleached and bleached-waved hair was then investigated. Hair swatches of each type of hair were prepared and each was then treated with one of the 5 per cent solutions. A water control and an hydroxyproline treated swatch were also included in the analysis. The treatment consisted of soaking for 10 min, blotting off the excess, and rinsing for 30 sec in warm running tap water.

To determine the amount of protein sorbed on the hair, the swatches were hydrolyzed with barium hydroxide, and the hair hydrolysate analyzed for hydroxyproline, the amino acid found in collagen protein but not in hair. In addition, the amount of hydroxyproline in each fraction was determined in order to correlate per cent hydroxyproline to per cent protein (6).

Ultracentrifugation

Two of the fractions separated by the Sephadex G-75 column were prepared for ultracentrifugation on a Beckman Ultracentrifuge* by diluting to 2 mg/ml in 0.25 *M* NaCl. This solution was placed in 1 side of a filled-Epon double sector synthetic boundary center piece,* and 0.25 *M* NaCl was placed in the other side. The cell with sapphire windows was placed in an AN-D rotor, and the run started. The conventional sedimentary equilibrium method of determining molecular weight was used. The experimental set-up for the 2 runs was as follows.

*Beckman Instruments Inc., Palo Alto, CA.

	Run One	Run Two
Fraction	1,000–5,000	5,000–30,000
Left sector	0.15 ml 0.25 *M* NaCl	0.15 ml 0.25 *M* NaCl
Right sector	0.15 ml 2 mg/ml protein in 0.25 *M* NaCl	0.12 ml 2 mg/ml protein in 0.25 *M* NaCl
Temperature	13.00°C	13.00°C
Speed		
Overspeed	52,000 rpm–4 h	44,000 rpm–3 h
Equilibrium speed	44,000 rpm–18 h	30,000 rpm–18 h

The molecular weights determined by ultracentrifugation were compared to the results obtained by gel filtration as will be shown later in this paper.

RESULTS

GEL FILTRATION

From the elution diagrams (absorbance versus elution volume) of each of the three hydrolysates studied, graphs of molecular weight versus per cent by weight were drawn. These graphs represent the molecular weight distribution curves for these proteins.

The elution diagrams, Fig. 1, are curves generated by the continuous flow spectrophotometer. These diagrams are used in preparing molecular weight distribution curves.

The enzyme hydrolysate was preserved with methylparabens and propylparabens, as well as benzalkonium chloride. These materials absorb at 280 nm and were eluted from

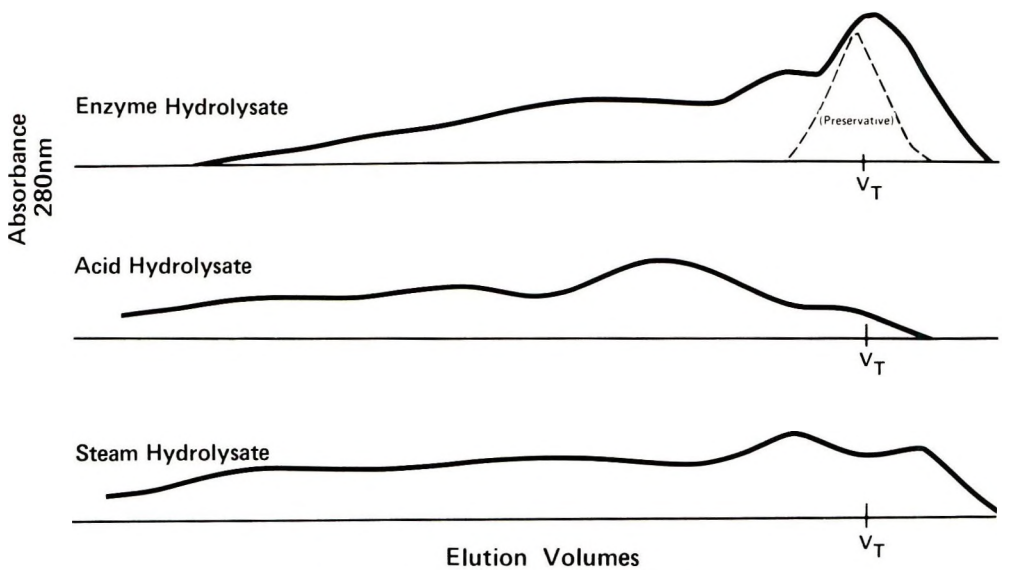

Figure 1. Elution diagrams, Sephadex G-75

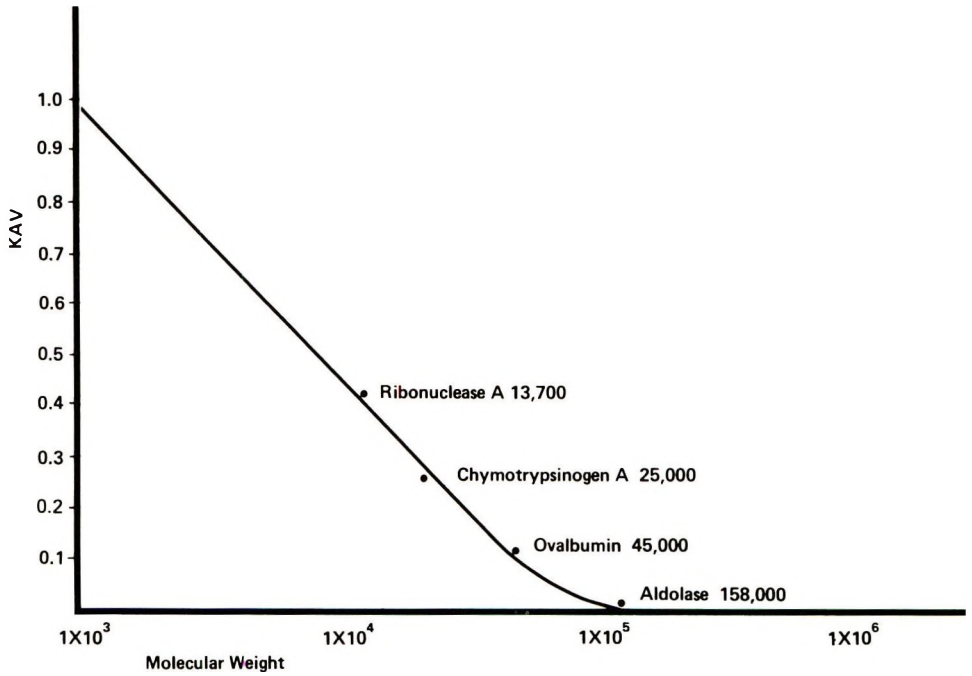

Figure 2. Calibration curve, G-75

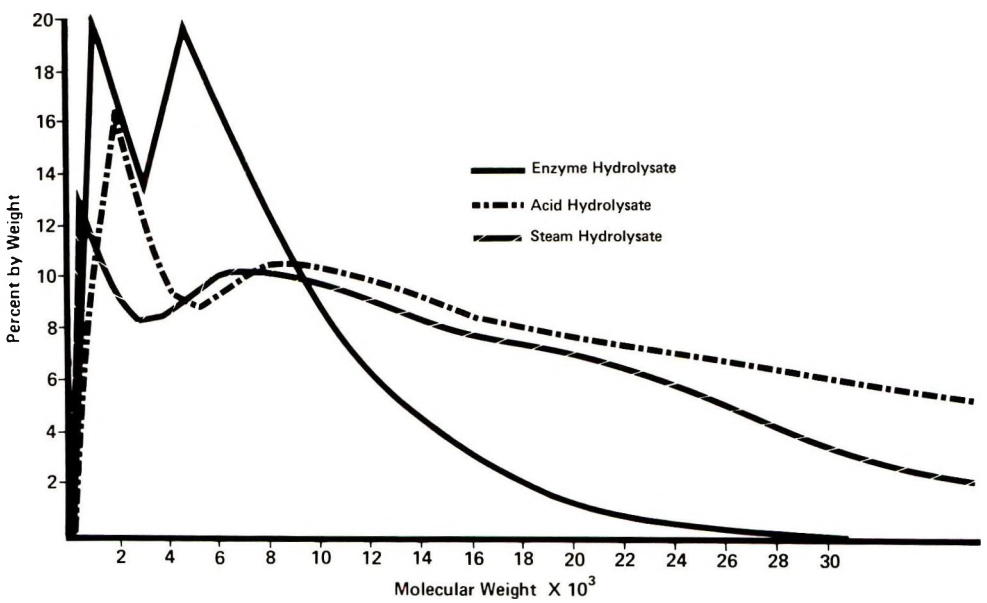

Figure 3. Molecular weight distribution curves

the column with the low molecular weight material. When preparing the molecular weight distribution curve of the enzyme hydrolysate, the absorbance due to the preservative had to be subtracted.

Figure 2 is the calibration curve, and shows the relationship of molecular weight to elution volume. The elution volume is expressed as Kav, which is the relationship of the elution volume to the void volume and the total bed volume.

$$Kav = \frac{Ve - Vo}{Ve - Vo}$$

As can be seen from the calibration curve, the elution volume has a straight line relationship to the logarithm of the molecular weight over most of the range between the void volume and the total bed volume.

From the elution diagrams and the calibration curve, molecular weight distribution curves were drawn. These graphs are shown in Fig. 3. These distribution curves are used to calculate both the weight average and the number average molecular weights.

The weight average and the number average molecular weights were calculated as follows.

$$M_n = \frac{P_i}{(P_i/M_i)}$$

where

M_w = weight average molecular weight
P = per cent of material at a constant elution volume interval
M_i = molecular weight at this interval $M_n = P_i/(P_i/M_i)$
M_n = number average molecular weight
P_i = percentage of material at a constant elution volume interval
M_i = molecular weight at this interval

In Table I the molecular weight averages calculated from the molecular weight distribution curves are shown.

ULTRACENTRIFUGATION

In Table II, the results of the ultracentrifuge run are compared to the gel filtration results.

Table I

Protein Hydrolysate	Weight Average	Number Average
Enzyme	4,000 ± 10 per cent	2,100 ± 10 per cent
Acid	9,300 ± 10 per cent	2,500 ± 10 per cent
Steam	7,800 ± 10 per cent	1,800 ± 10 per cent

Table II
Molecular Weight Ultracentrifugation versus Gel Filtration[a]

Gel Filtration	Ultracentrifugation
Over 5,000	8,700 – 3,600
5,000 – 1,000	3,000 – 1,500

[a]The molecular weights measured by these 2 methods correlate closely.

Table III

Fraction	Hair Type	Protein Substantivity mg Protein/100 g Hair
Greater than 30,000	Bleached	140
	Bleached-waved	300
30,000–5,000	Bleached	50
	Bleached-waved	290
5,000–1,000	Bleached	80
	Bleached-waved	370
Less than 1,000	Bleached	200
	Bleached-waved	510
Hydroxyproline	Bleached	40
	Bleached-waved	100

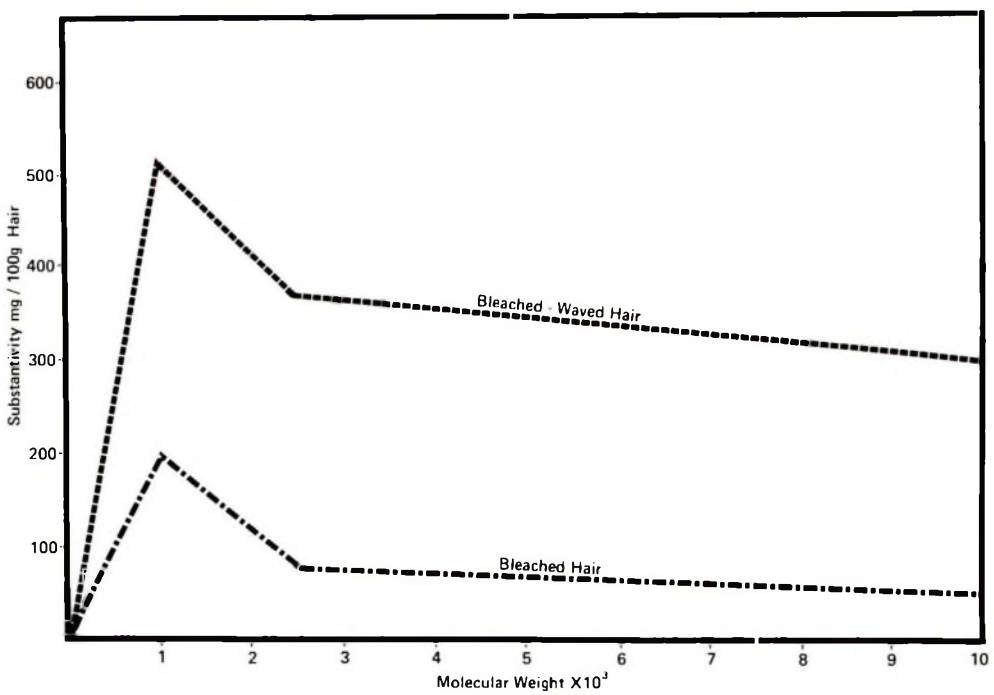

Figure 4. Substantivity of various molecular weight fractions

PROTEIN SUBSTANTIVITY

The relationship of molecular weight to protein substantivity is shown in Table III. The data in Table III show that peptides of molecular weight of about 1,000, but greater than the molecular weight of amino acids, gives the highest substantivity. Figure 4 shows the results in Table III graphically.

CONCLUSION

A study of the molecular weight distributions of 3 protein hydrolysates used in cosmetics was conducted. The effect of molecular weight on protein substantivity to damaged hair was also investigated in an attempt to find a relatively narrow weight range that gives optimum substantivity. Two conclusions can be drawn. (1) papain hydrolysis results in a narrow distribution of molecular weights. About 75 per cent of the molecules have weights between 500 and 10,000. As opposed to enzymatic hydrolysis, the acid and steam hydrolysates have much broader distributions. Seventy-five per cent of the molecules range in weights between 500 and 30,000. (2) The data have shown that polypeptides of molecular weight of about 1,000 but greater than the molecular weight of amino acids give the highest substantivity to damaged hair.

These conclusions are based on a preliminary study and a number of points still remain unresolved. Answering these questions will involve a more detailed separation of the molecules below molecular weight 1,000 and an in-depth study of their effect on substantivity. Separating polypeptides of molecular weight 0 to 1,000 is difficult. Gel filtration chromatography can be used, however, calibrating the column can pose a problem. Until these lower molecular weights are investigated, the conclusions that have been stated are rather broad. It will be the purpose of subsequent studies to narrow down the molecular weight range necessary for optimum substantivity.

Molecular weight has been thought to be an important feature of cosmetic protein hydrolysates. It was generally assumed that lower molecular weight polypeptides were more substantive to damaged hair. The study reported here has shown that peptides in the range of molecular weight 1,000 are more substantive than the very high molecular weight polypeptides.

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Society of Cosmetic Chemists Award Sponsored by Perry Brothers Fragrances, Div. of Mallinckrodt, Inc.

The Society of Cosmetic Chemists Award sponsored by Perry Brothers Fragrances, Div. of Mallinckrodt, Inc., was presented by Dr. S. Mark Henry, Bristol-Myers Products, for his outstanding contributions to cosmetic science and technology in the field of microbiology during 1976.

An inscribed scroll and a $2,000 honorarium were presented formally by Dr. Karl Laden, Society of Cosmetic Chemists President, at the Awards Luncheon held May 5 at the Hotel Bonaventure in Montreal, Canada.

Left to right: Dr. Karl Laden, SCC President; Dr. S. Mark Henry, Bristol-Myers Products, Awardee

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Prediction of optimum O/W emulsification via solubilization measurements

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Synopsis

In the course of investigating the effects of SURFACTANT LOCATION on O/W EMULSIFICATION, it was discovered that there existed a useful correlation between the maximum amount of aqueous phase that could be solubilized in the oil phase containing the emulsifier and the average droplet size of the emulsion subsequently formed. Experiments were carried out with liquid hydrocarbons and many other oils frequently used in cosmetic emulsions. The emulsifiers used included various nonionic, anionic, cationic surfactants, and their mixtures. Analysis of the solubilization measurements and microphotographically obtained emulsion droplet size distribution data clearly indicated that the point of optimum O/W emulsification, i.e., the point where the finest O/W emulsion was formed in emulsifying with a series of surfactant mixture, corresponded to the point of maximum solubilization provided that the latter fell in a region where O/W emulsion formation was possible. In some systems studied, the maximum solubilization points were found in the region where only W/O emulsions could be formed under the experimental conditions. In such a case, the optimum O/W emulsions were generally found near the W/O–O/W transition point. The correlation held quite well in spite of the differences in the type and ionic nature of the surfactants employed.

INTRODUCTION

In spite of the recent advances in colloid and surface chemistry, the technique of emulsion formulation and manufacturing remains very much an art. Although, it has been 27 years since Griffin (1,2) first proposed the HLB (hydrophile–lipophile balance) method, the selection of an emulsifier system for a practical cosmetic emulsion still requires a tedious trial-and-error procedure. This is chiefly due to the extremely complex nature of emulsions, which often defies systematic scientific treatment.

Fundamentally, HLB is a very useful system in classifying surfactants according to their hydrophilic/lipophilic characteristics. It is, also, recommended as a tool for selecting efficient emulsifiers for preparing emulsions; nevertheless, in this respect, there are many shortcomings which hinder its practical applications.

First of all, to use HLB method for emulsification, one needs not only the "HLB" values of the surfactants but also the "required HLB" values of all the oil phase components to be used in the emulsion. Unlike the HLB values of the surfactants, the

available data on required HLB values are quite limited and the published values are often conflicting. This is partly due to the fact that there is still a lack of a reliable and accurate method to determine the required HLB value of an oil (3).

Second, even for the oils for which required HLB values are available, the HLB method provides only a very rough guide in finding a right emulsifier combination. Even if a formulator knows that he requires a certain HLB to emulsify a given oil, he still needs to carry out many trial-and-error emulsifications, using combinations of surfactants with different chemical types before finding a suitable combination for his practical purpose. The HLB method provides no further guidance in this respect.

Third, the HLB method assumes that like HLB values of the surfactants, required HLB values of oils are also linearly additive. This linear relationship has been found to be questionable in many oil mixtures (4). Furthermore, Griffin's HLB method assumes that both the HLB value of a surfactant and the required HLB value of an oil are *constants* independent of other parameters. This assumption makes the HLB method quite simple to use; however, it also makes the method less precise and sometimes unreliable, since many other factors such as aqueous phase additives, surfactant concentration, phase volume of the oil, emulsification temperature, or even the preparative method can influence the hydrophilic/lipophilic characteristics of emulsions (5,6,7).

Furthermore, the HLB method works fairly well if one uses only ethoxylated nonionic surfactants to emulsify hydrocarbons. It often fails to work satisfactorily, however, in many practical cosmetic emulsions containing a complex mixture of oils, fatty materials, polar substances, and various surfactants. Clearly, there is a need for a better system to aid emulsion formulators to select the most efficient emulsifier combination from the great number of commercial surfactants available today.

During the course of investigating the effects of surfactant location and migration on emulsion properties, it was discovered that there appeared to be a correlation between the maximum amount of the aqueous phase which could be solubilized in the oil phase containing the emulsifiers, and the average droplet size of the emulsion subsequently formed. For a given pair of surfactants, one relatively hydrophilic and the other relatively lipophilic, the most efficient emulsifier combination was generally found at the point where there was the greatest amount of solubilization. After testing over 100 systems with varying oils, surfactants, and other additives, it is believed that this correlation can be very useful in aiding emulsion formulation and to minimize the need for a trial-and-error procedure.

EXPERIMENTAL

For low-speed emulsification, emulsions were prepared by first dispersing the surfactants in the oil phase using a mixer. Sixty-five g of aqueous phase was first placed in a 200 ml beaker, and 35 g surfactant-oil mixture was carefully placed on the top. A 2×6 cm flat blade paddle mixer, set 5 mm above the bottom of the beaker, was turned on immediately to start emulsification. In most experiments, the emulsification was done at room temperature ($21° \pm 1°C$), and the emulsions were mixed for 3 min at exactly 150 rpm before droplet size measurements. For high-speed emulsification, a rotary homomixer was used. All emulsification operations were carefully done to assure good reproducibility.

Emulsion droplet size distribution was determined from the Polaroid* pictures taken through an optical microscope. The amount of aqueous solubilization was determined by adding the aqueous phase, drop by drop, into the oil phase containing the surfactant while constantly mixing with a magnetic stirrer. The first sign of permanent turbidity was taken as the end point and the total amount of the aqueous phase added was recorded. In cases where a complete solubilization phase diagram was desired, the oil phase was placed in a large number of capped vials and shaken with varying amounts of water. After equilibration, the vials were observed for any sign of separation or turbidity and a phase diagram was constructed.

RESULTS AND DISCUSSION

CORRELATION OF EMULSIFICATION EFFICIENCY WITH SOLUBILIZATION

There were 2 main purposes in this investigation. The first was to determine the validity and scope of the correlation between the efficiency of emulsification and the maximum amount of aqueous solubilization by the oil phase containing the surfactants. The second aim was to investigate the fundamental role of the solubilization process and its relationship with emulsification.

In this work, emulsification efficiency refers to the efficiency with which a surfactant or a mixture of surfactants emulsify the oil phase to form an emulsion without the use of high-shear equipment. A more efficient surfactant is defined as one which produces an emulsion with a finer average droplet size than a less efficient one under the same degree of mechanical agitation. Generally speaking, an emulsion with a smaller average droplet size is more stable than one with a larger droplet size. However, for this investigation, the emulsification efficiency was directly expressed in terms of droplet size distribution immediately after emulsification rather than the emulsion stability. This choice was made in order to avoid possible confusion in interpreting the data, since emulsion stability is not only a function of droplet size, but also of many other parameters such as the viscosity of the external phase which is often influenced by the presence of the surfactants.

In preparing most emulsions, a moderate mixing speed (150 rpm) was used. The use of an excessively high mixing speed would promote the break-up of droplets caused by mechanical shear and obscure the real effects of the emulsifiers.

The correlation appears to hold both for O/W emulsions prepared with single surfactants and also the emulsions made with combinations of two surfactants, one relatively hydrophilic, and the other relatively lipophilic.

Figure 1 is an example of the data obtained with a series of ethoxylated nonylphenols with ethylene oxide ranging from 2 to 20 moles. Strictly speaking, these are not single surfactants, since they are commercial materials which are expected to have a wide ethylene oxide distribution range. Solubilization limit was defined as the maximum amount of water in milliliters which could be solubilized into a total of 100 g of oil-surfactant mixture. The abscissa represents the average weight percentage of the

*Polaroid Corp., Cambridge, MA.

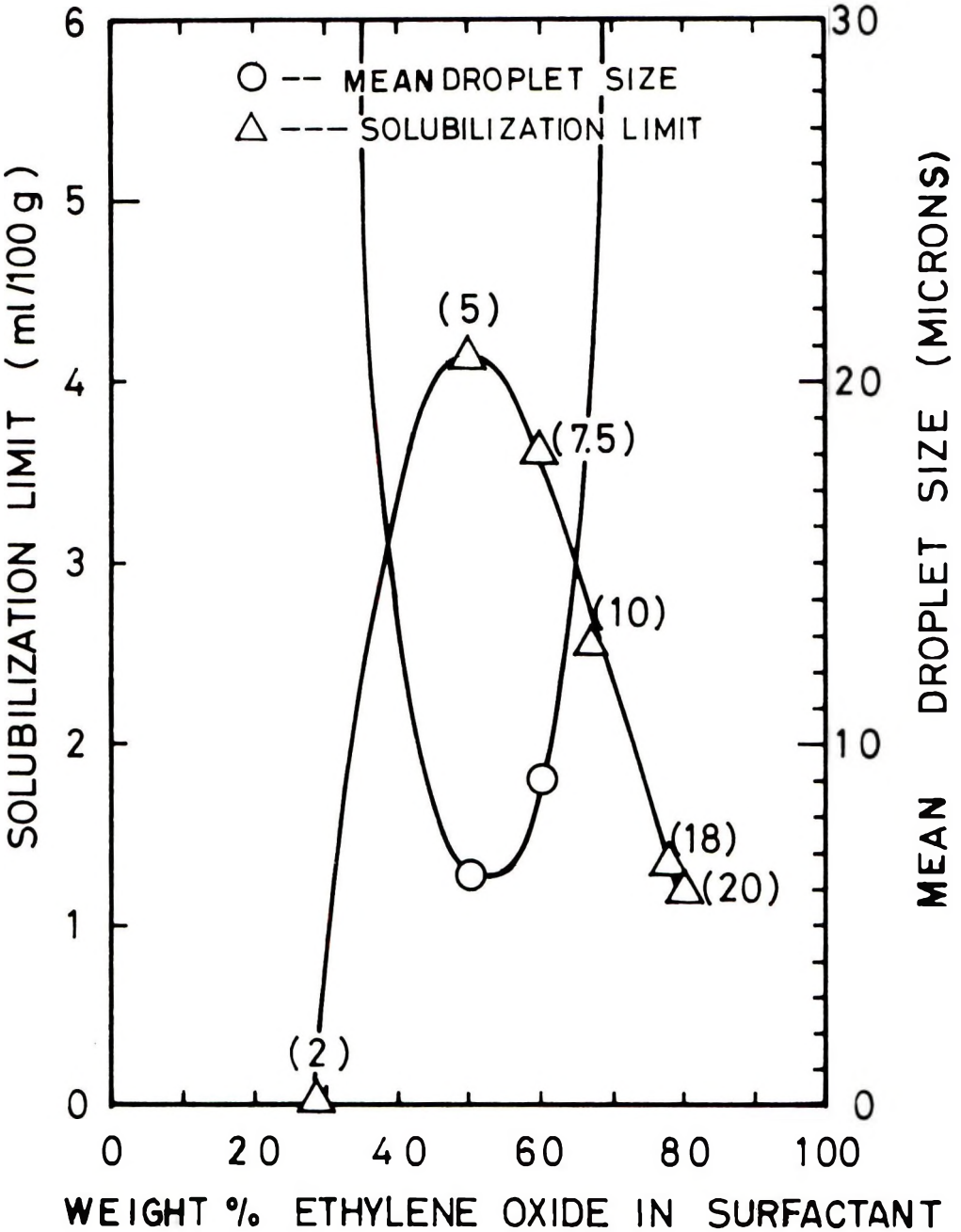


Figure 1. Solubilization-emulsion droplet size correlation for single surfactant systems. (Emulsion contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent polyoxyethylene nonylphenyl ethers with per cent ethylene oxide corresponding to abscissa. Number in parenthesis indicates actual mole number of E. O. in each surfactant)

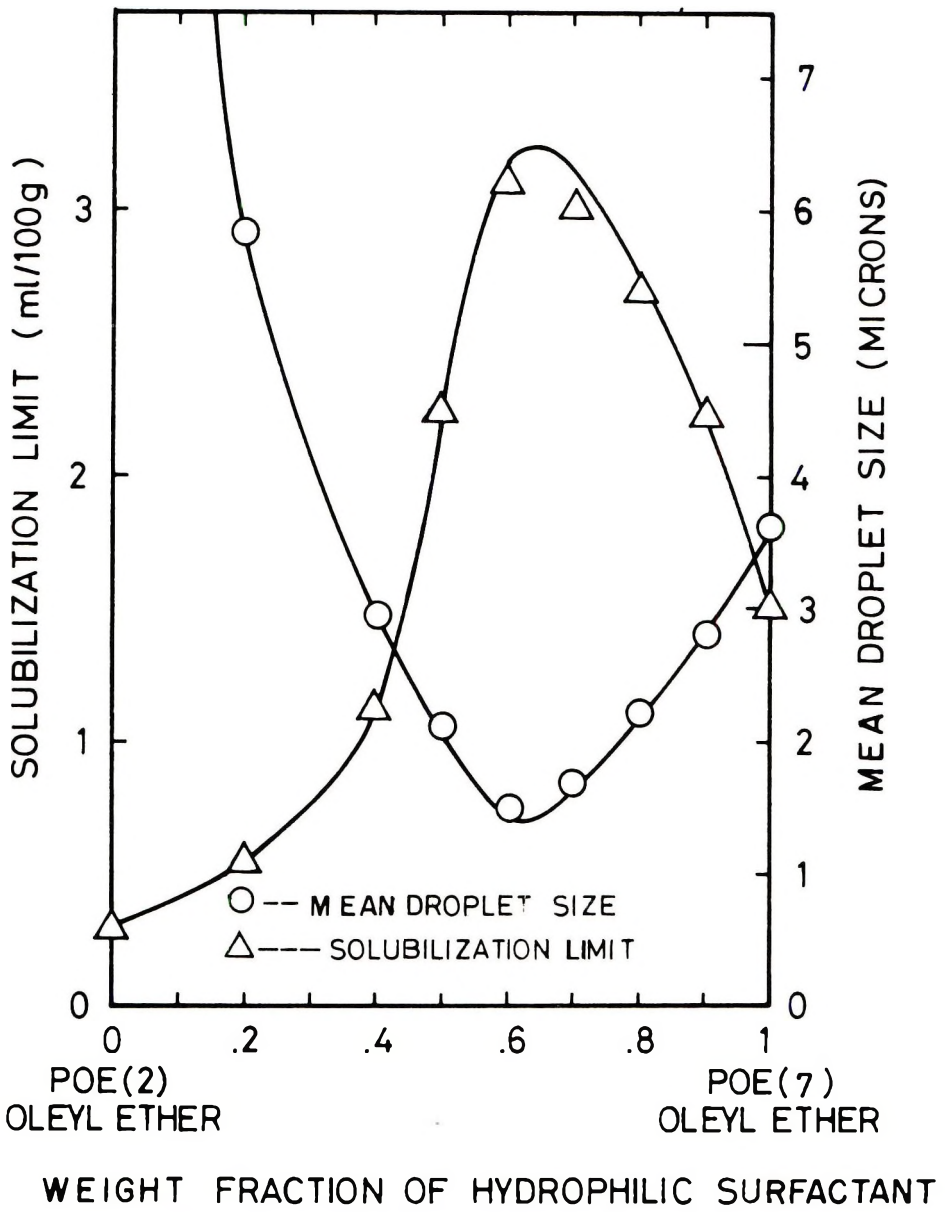


Figure 2. Solubilization-emulsion droplet size correlation for binary surfactant systems. (Emulsions contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent nonionic surfactant mixtures. Surfactant mixtures consist of hydrophilic POE (7) oleyl ether and lipophilic POE (2) oleyl ether at ratios indicated by abscissa)

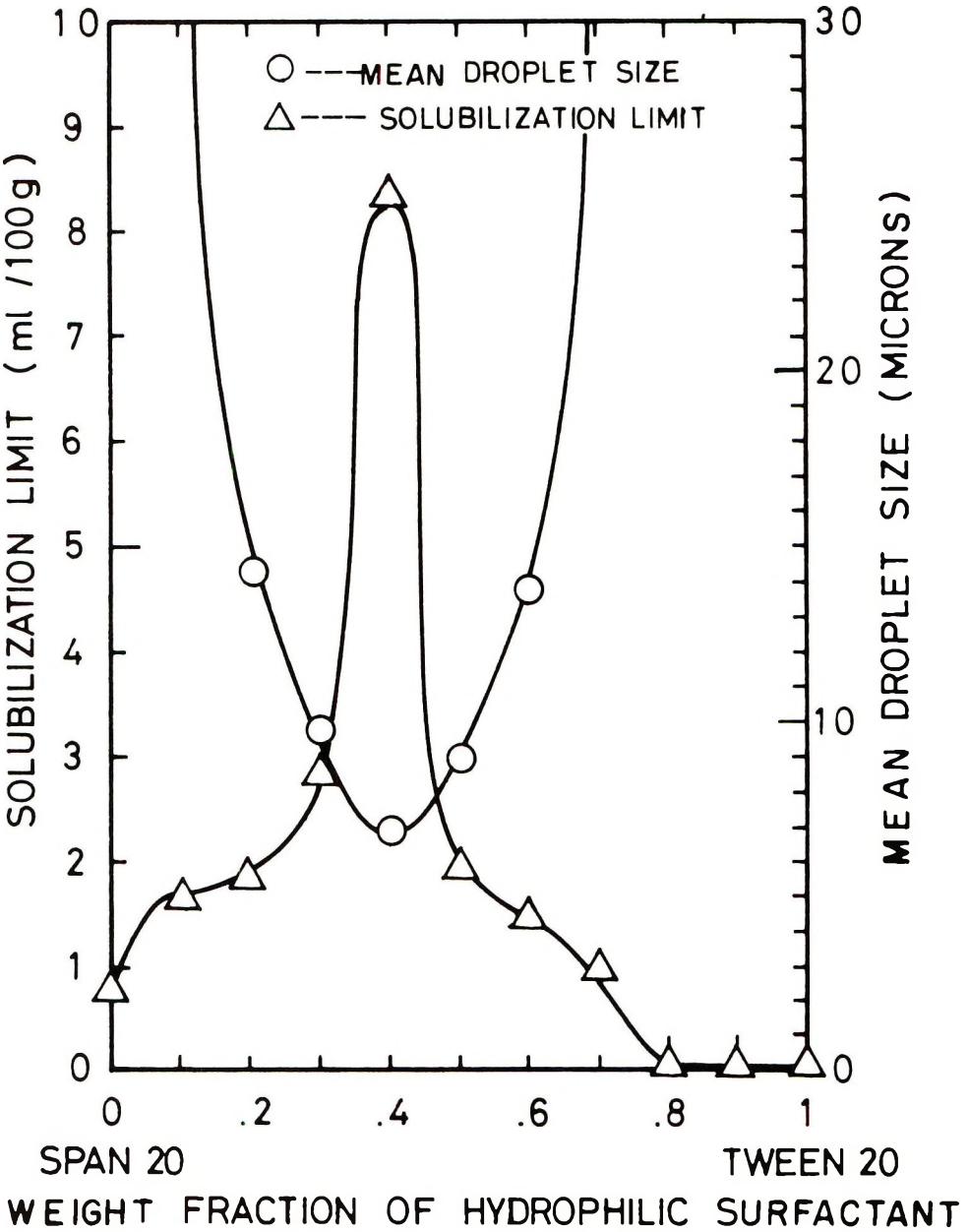


Figure 3. Solubilization-emulsion droplet size correlation for binary surfactant systems. (Emulsions contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent nonionic surfactant mixtures. Surfactant mixtures consist of hydrophilic Tween 20 and lipophilic Span 20 at ratios indicated by abscissa)

ethylene oxide in the surfactant. The average droplet sizes of the emulsions obtained from the microphotographic measurements were also indicated in Fig. 1.

It is clearly seen from Fig. 1 that a maximum solubilization in this series of surfactants was obtained when the 5 mol ethylene oxide adduct was used and that this surfactant also gave an emulsion with finest mean droplet size.

Figure 2 shows a similar correlation obtained with various mixtures of 2 and 7 mole ethylene oxide adducts of oleyl ether. Here again, a good correlation between the maximum solubilization point and the minimum droplet size was obtained. The HLB of the surfactant blend at the optimum point was 9.7 calculated from the supplier's experimentally determined HLBs of the 2 and 7 mole adducts, which were given as 7.7 and 10.7, respectively.* This value is fairly close to the literature value of the required HLB of paraffinic mineral oil which is about 10.

Figure 3 shows another example of mineral oil emulsion emulsified with combinations of Tween 20 and Span 20. Here again, a good correlation was obtained at Tween 20/Span 20 ratio of about 40/60. In most systems, the solubilization data were obtained through drop-by-drop addition of water into the oil-surfactant mixture with mixing as described earlier. In a few systems, the solubilization curves were carefully studied by shaking varying amounts of water into vials containing the oil-surfactant mixtures and equilibrating the systems before making observations. Figure 4 shows a photograph taken shortly after the preparation of the representative vials used in the Tween 20-Span 20 system.

TESTING OF THE CORRELATION

In order to test the validity of the correlation, many different types of surfactants, oils, and other additives were employed for solubilization measurements and corresponding emulsification experiments.

In addition to nonionic surfactants, anionic and cationic surfactants and their combinations were also tested. The data for an anionic-nonionic system using 96 per cent active sodium dioctyl sulfosuccinate (SDOS)† and sorbitan monooleate (Arlacel 80)‡ are shown in Figure 5. A fairly good correlation is apparent for this mixed-surfactant system as both the solubilization peak and the droplet size minimum are located around 0.6 weight fraction. It is noted that below approximately 40 per cent of SDOS, the emulsification became extremely poor due to the phase inversion. The point of phase inversion is indicated by the vertical dashed line.

In most of the systems tested, the phase inversion occurred at points near the left end of the diagram and sufficiently removed from the solubilization peaks so that practically no effect on the correlation was observed. However, in some systems, the phase inversion boundary fell on or near the peak as illustrated by Figure 6 which em-

*These are the values given by Nikko Chemicals Co., Ltd. The HLB values of similar surfactants given by ICI United States Inc., are 4.9 and 10.7, respectively. This would give the HLB at the optimum point as 8.7.
†Tokyo Kasei Kogyo Co., Ltd. of Tokyo, Japan.
‡Kao-Atlas Co., Ltd. of Tokyo, Japan.

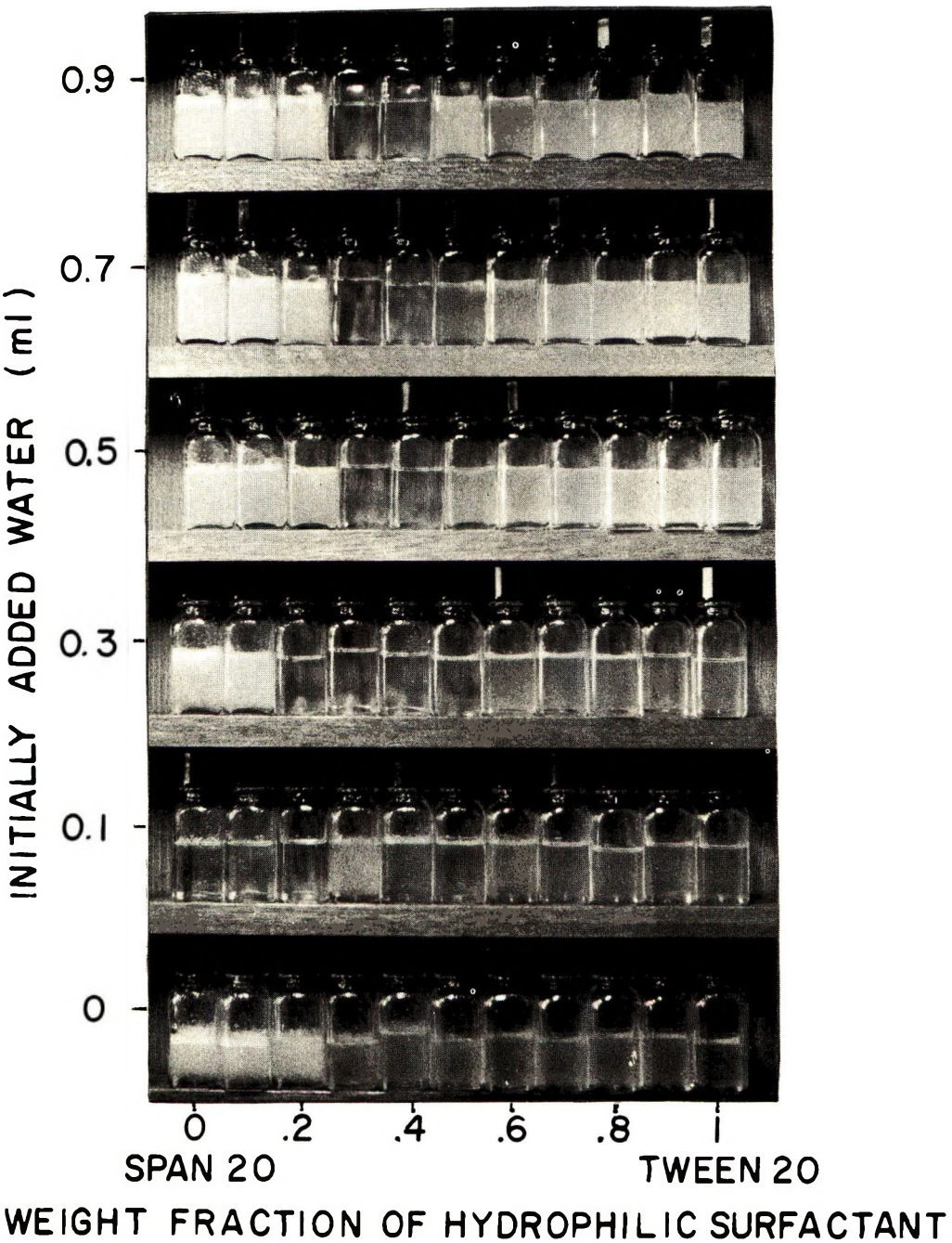


Figure 4. Photograph of vials containing surfactant-oil mixtures. (Each vial contains 15 g mineral oil, 2.5 g mixture of Tween 20 and Span 20, and small amounts of deionized water. Amounts of water in milliliters are indicated by numbers on left-hand edge of photograph. Weight fractions of Tween 20 in the surfactant mixtures are printed under bottom row of vials)

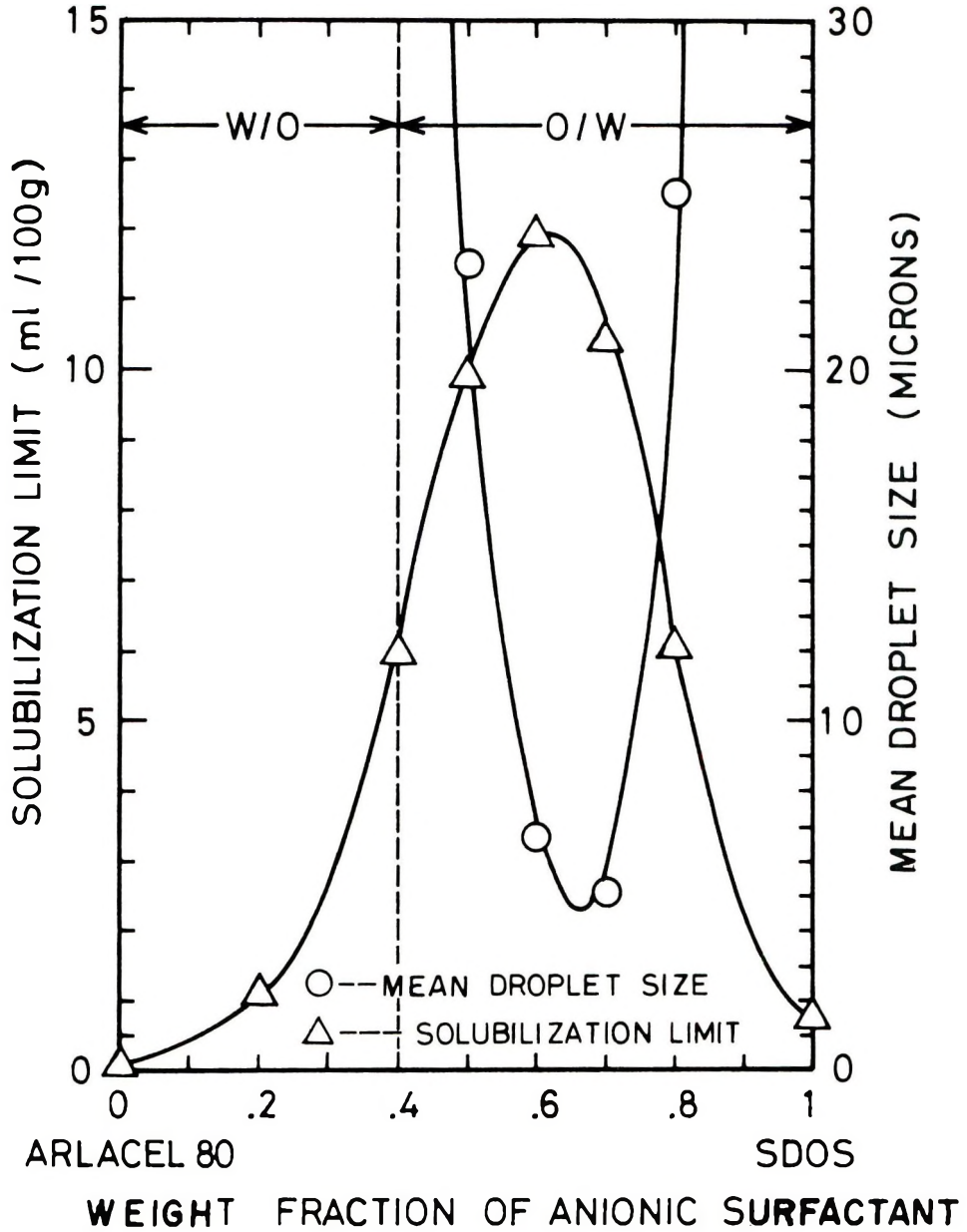


Figure 5. Solubilization-emulsion droplet size correlation for anionic-nonionic systems. (Emulsions contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of hydrophilic anionic sodium dioctyl sulfosuccinate, and lipophilic Arlacel 80 at ratios indicated by abscissa)

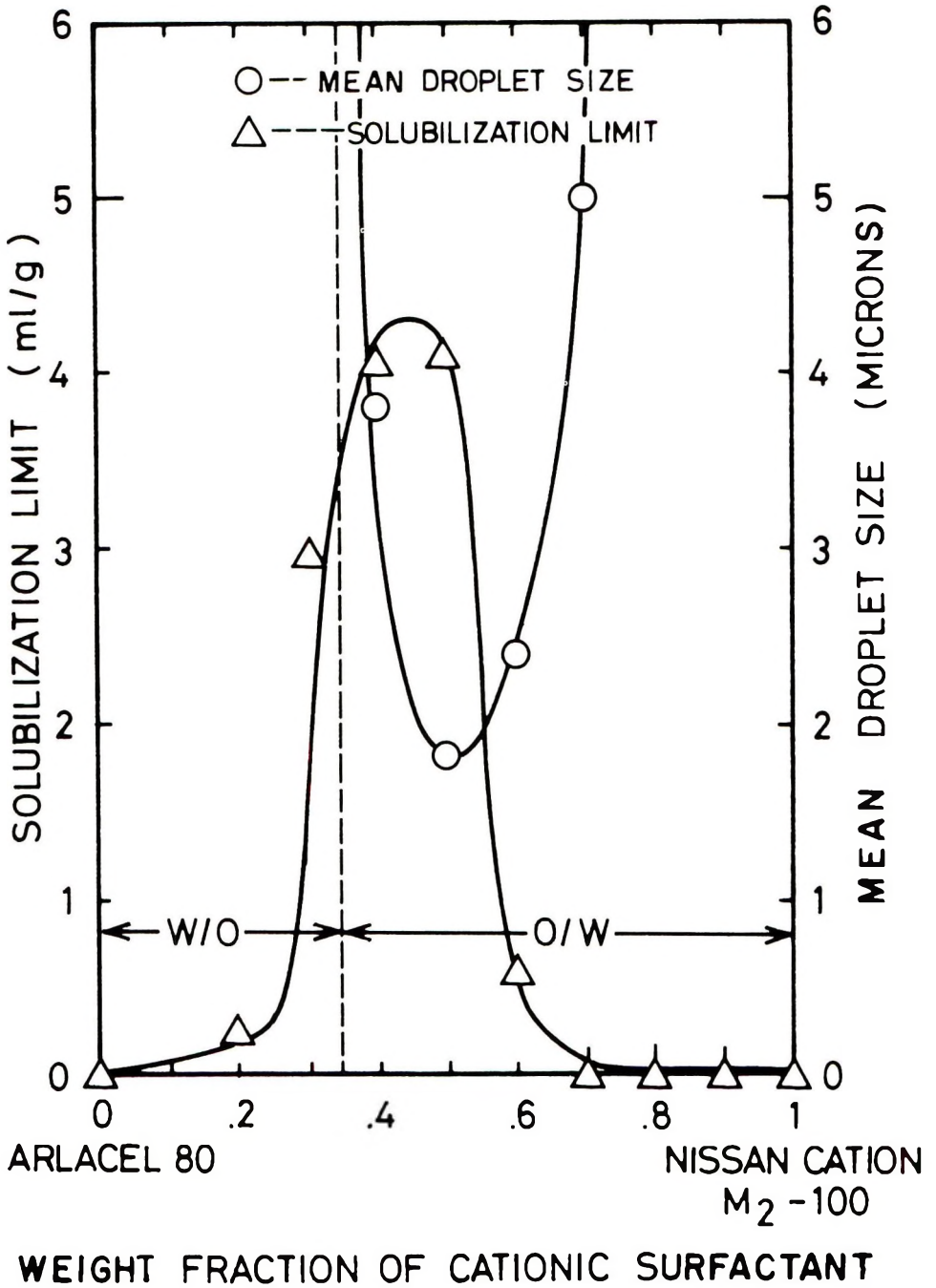


Figure 6. Solubilization-emulsion droplet size correlation for cationic-nonionic systems. (Emulsions contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of hydrophilic cationic lauryl dimethyl benzyl ammonium chloride and lipophilic Arlacel 80 at ratios indicated by abscissa)

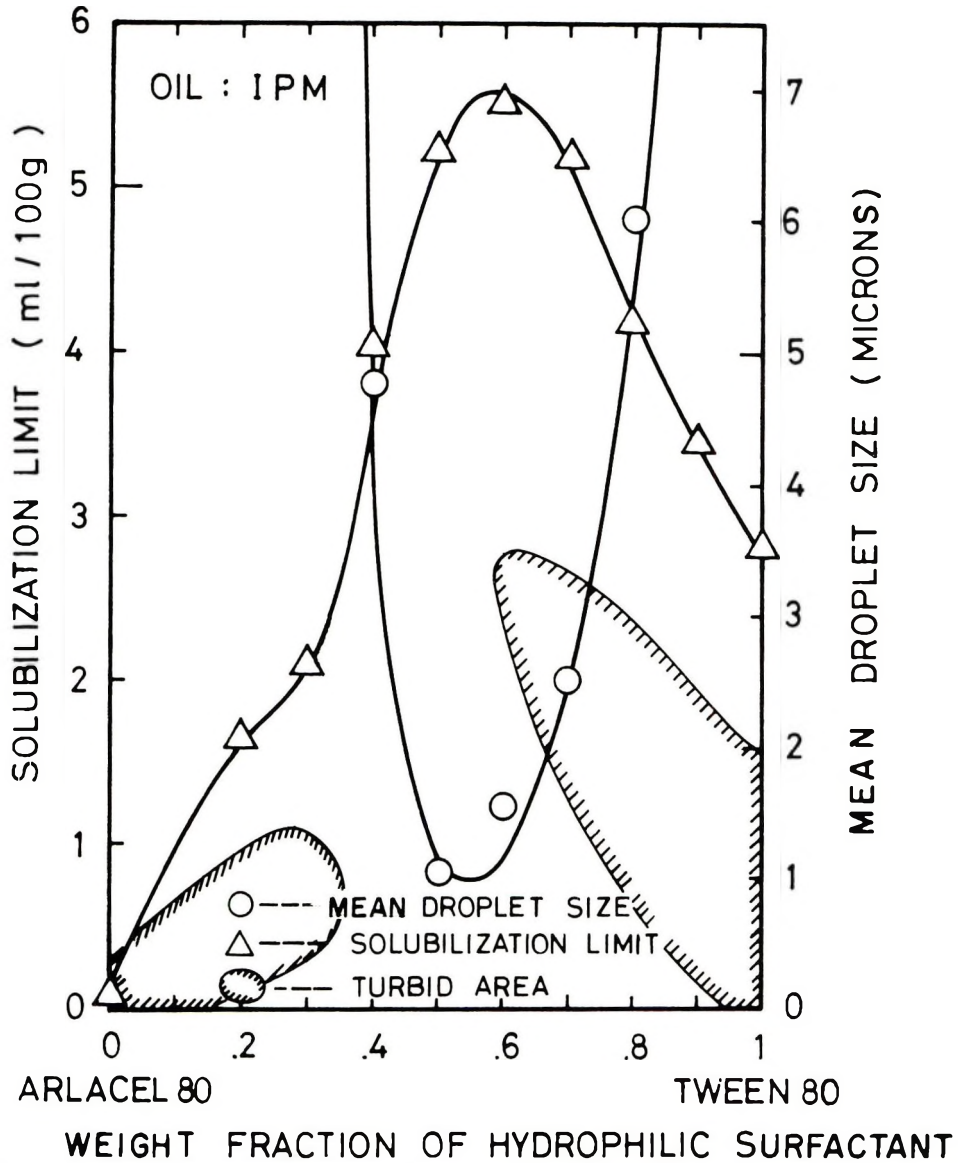


Figure 7. Solubilization-emulsion droplet size correlation for isopropyl myristate systems. (Emulsions contain 30 per cent IPM, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of hydrophilic, Tween 80, and lipophilic Arlacel 80 at ratios indicated by abscissa)

ployed a cationic-nonionic surfactant combination. The surfactants used were lauryl dimethyl benzyl ammonium chloride* and Arlacel 80. In this example, the point of optimum emulsification does not precisely coincide with the solubilization peak, but is located somewhat to the right of the peak. This is clearly due to a phase inversion, from O/W to W/O, taking place near the solubilization peak.

In addition to mineral oil, many other oils commonly used in cosmetics were tested. Figure 7 gives an example using isopropyl myristate (IPM) and nonionic surfactants. The phase diagram for this system is somewhat more complex due to the appearance of turbid areas under the solubilization curve. In this case, however, the turbid areas did not affect the correlation. In other more complex systems, as will be explained later, the turbid areas could shift the point of optimum emulsification.

The use of the HLB method often does not work satisfactorily in many emulsions containing polar oils. It is believed that a part of the problem is probably related to a flaw in the basic concept. The "HLB-required HLB" emulsifier selection method implicitly divides an emulsion into two parts: a surfactant or a surfactant mixture which is *to emulsify,* and an oil or oil mixture which is *to be emulsified.* In dealing with raw materials for practical emulsions, however, it is not always possible to make such a clear distinction.

For example, lanolin is generally regarded as an oil, but it can also serve as a low HLB emulsifier. Fatty alcohols or fatty acids are commonly used cosmetic ingredients for the oil phase, but they are surface active and can be adsorbed at the oil-water interface. If one considers them as oils to be emulsified, then their required HLB values must be used to calculate the required HLB of the entire oil phase. If one considers them as surfactants, then their HLB values must be included in the surfactant mixture. The problem is that one does not get a consistent result by interchanging the HLB, required HLB values, indicating that there is an inherent inconsistency in this system. This can be best illustrated by considering the following example.

Suppose that it is desired to emulsify an oil mixture consisting of 800 g mineral oil and 200 g cetyl alcohol, using a blend of Tween 80† and Arlacel 80‡.

If one first regards cetyl alcohol as an oil, the "required HLB" of the oil mixture is calculated as follows (8): required HLB of mineral oil, paraffinic = 10; required HLB of cetyl alcohol = 15. Therefore, required HLB of the oil mixture = 0.8 (10) + 0.2 (15) = 11.

Taking the HLBs of Tween 80 and Arlacel 80 as 15 and 4.3, respectively (8), one readily determines the optimum ratio of Tween 80/Arlacel 80 for this mixture to be 1.67. If the total amount of the nonionic surfactants is to be 100 g, one needs 62.6 g Tween 80 and 37.4 g of Arlacel 80 to emulsify the cetyl alcohol-mineral oil mixture according to the HLB method.

Alternatively, if one should regard the 200 g cetyl alcohol as a low HLB emulsifier and

*Nissan Cation M_2-100 by Nippon Oils and Fats Co., Ltd., Tokyo, Japan.
†Polyoxyethylene (20) sorbitan monooleate, ICI United States, Inc.
‡Sorbitan monooleate, ICI United States, Inc.

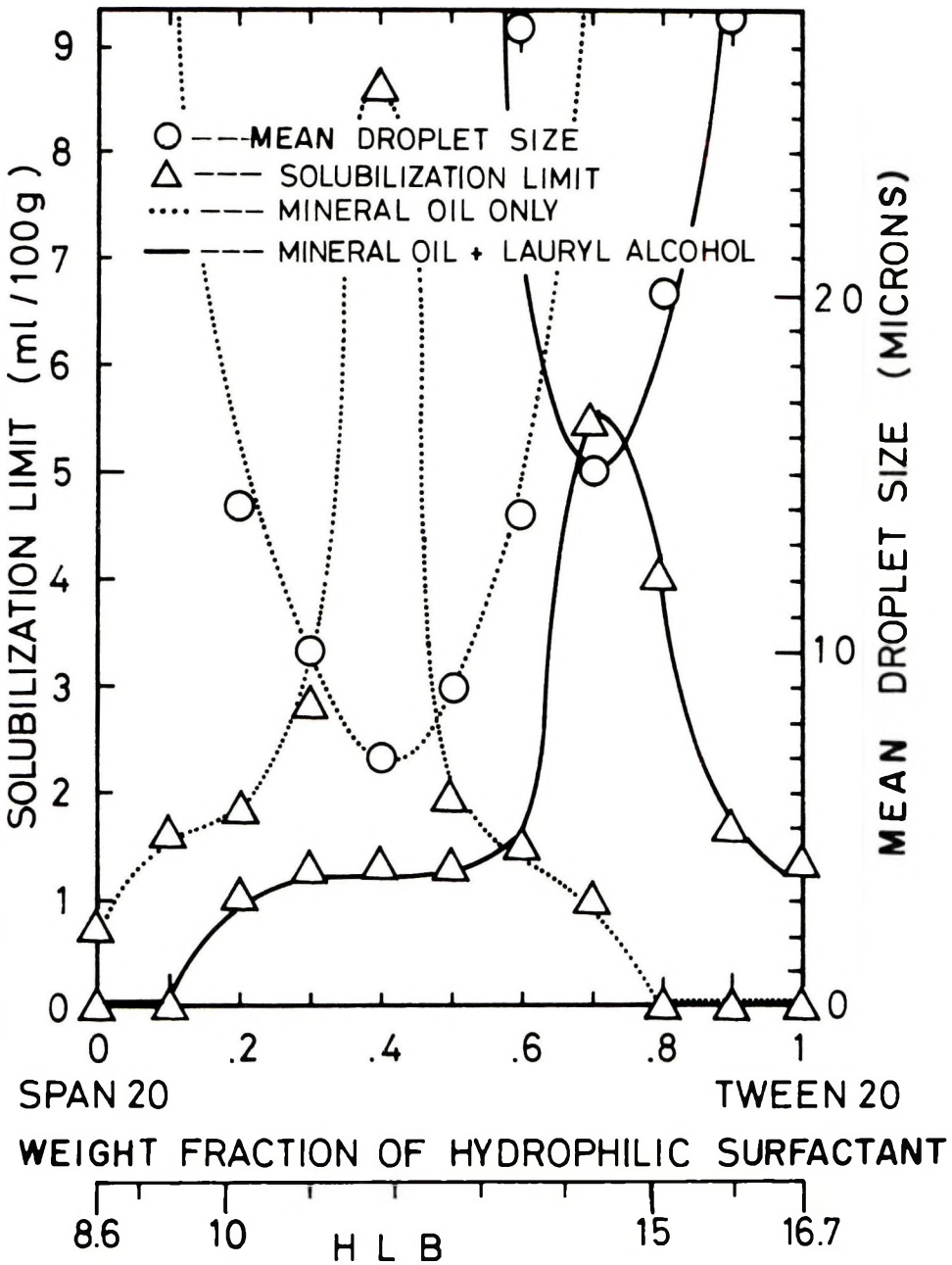


Figure 8. Shifting of optimum emulsification peak by addition of lauryl alcohol. (Emulsions contain 30 per cent oil phase, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of hydrophilic Tween 20 and lipophilic Span 20 at ratios and corresponding HLB values indicated by abscissa. Dotted lines represent data for pure mineral oil systems. Solid lines represent data for oil mixture consisting of 8 parts mineral oil and 2 parts lauryl alcohol)

use the literature HLB value of 1.15* to repeat the above calculations, one would end up with a result requiring no Arlacel 80 but a very large amount, 354 g, of Tween 80 for the optimum emulsification. This means that by merely altering the functional concept of a component, one can come up with a vastly different surfactant requirement.

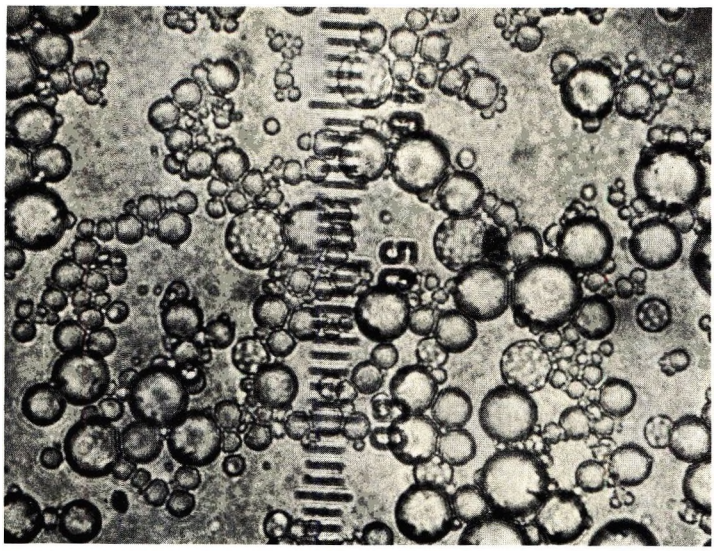
This is a serious problem, since there are so many common cosmetic ingredients like cetyl alcohol, which can be regarded either as oils or auxiliary emulsifiers. In reality, these materials probably function partially as an emulsified oil and partially as surfactant in practical emulsions. In the HLB system, however, one is forced to regard them either as a surfactant to emulsify or an oil to be emulsified, but unfortunately, these 2 alternatives do not lead to a consistent result. This is probably one of the main reasons why the HLB method does not work well for many practical emulsions containing polar substances.

The fact that the addition of a polar oil to a nonpolar oil often affects the required HLB of the system far more than that can be predicted from the simple additive rule can be demonstrated by considering the required HLB of lauryl alcohol which is given in the literature as 14 (8). Thus, a 20/80 mixture of lauryl alcohol/mineral oil has a required HLB value of 10.8 using the linear additivity rule, taking the required HLB value of mineral oil as 10. This means that one should expect no more than 1 unit shift of the required HLB by substituting 20 per cent of mineral oil with lauryl alcohol. However, our emulsification experiments with mixed oils indicated that the shift was considerably greater than one unit. In Fig. 8, the dotted lines indicate the solubilization and emulsification curves for pure mineral oil emulsions prepared with Tween 20 and Span 20. The solid lines on the same figure present the results of substituting 20 per cent of mineral oil with lauryl alcohol. It is clear that the optimum emulsification point shifted about 2.4 HLB units after adding lauryl alcohol to the nonpolar mineral oil. The maximum solubilization point also shifted to the right by the same proportion indicating the reliability of the solubility measurement as a means to predict optimum emulsification. Similar experiments with other polar oils such as oleyl alcohol or oleic acid indicate that the solubilization method can reliably predict the optimum emulsification point even in cases where the HLB system failed.

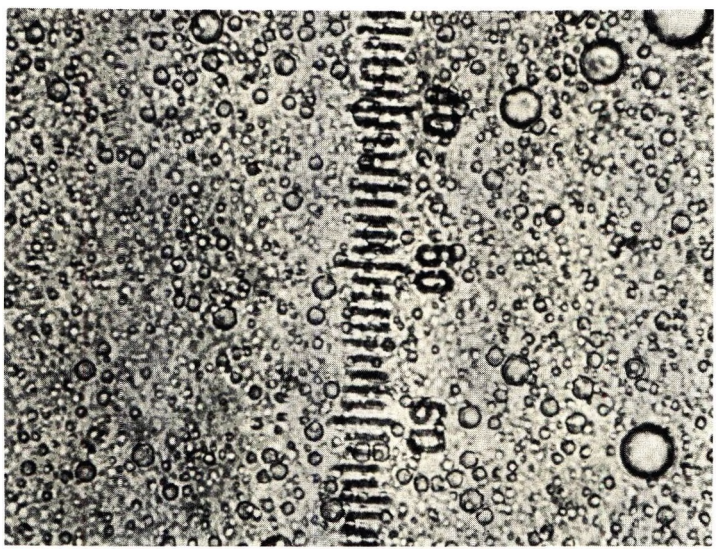
RELATIONSHIP WITH EMULSIFICATION MECHANISMS

In our previous work, we attempted to explain a dramatic difference in O/W emulsification efficiency due to the initial locations of the hydrophilic surfactants by proposing 2 separate mechanisms in emulsification (9). According to our hypothesis based on experimental evidences, mechanism A, which is the mechanism that produces the finer emulsion, *can* control emulsification when a relatively hydrophilic surfactant is initially disssolved in the oil phase. As water is added to this oil-surfactant mixture to start emulsification, the water is first solubilized in the oil phase and a W/O emulsion is formed. As more water is added, the hydrophilic surfactant starts to migrate to the aqueous phase resulting in an emulsion phase inversion to form an O/W emulsion. A short-lived double emulsion of (W/O)/W type may be formed during the transition stage. The phase inversion results in a production of emulsion with a fine droplet size.

*The experimental value of the HLB of cetyl alcohol is given as 1.0 while the calculated HLB according to Davies' group number is 1.3 (5). The average value of 1.15 is used in this calculation.



(A)



(B)

Figure 9. Microphotographs showing improvement of emulsification by adding 2 per cent water to make the oil phase homogeneous. (Emulsions contain 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of Tween 80 and Arlacel 80 at 80/20 ratio.): (A) emulsion made with nonhomogeneous oil phase (× 1200); (B) emulsion made with homogeneous oil phase containing 2 per cent water (× 1200)

When the surfactant is placed in the aqueous phase, phase inversion does not take place, and the oil droplets are broken up by the mechanical shear provided by the mixer. This was referred to as mechanism B, and unless a relatively high speed is used to process the emulsion, the resulting emulsion will have a much larger average droplet size than the same formulation prepared via mechanism A.

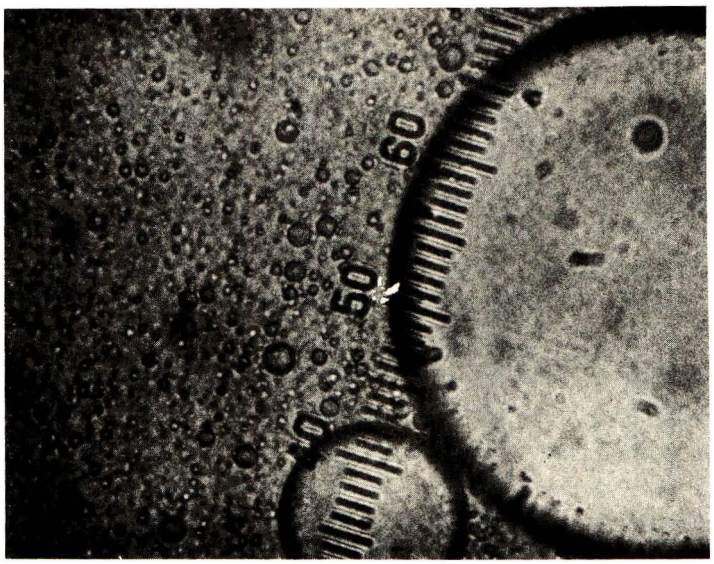


Figure 10. Microphotographs showing mineral oil emulsions with 2 distinct droplet size distributions. (Emulsion contains 30 per cent mineral oil, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of POE (10) oleyl ether and POE (2) oleyl ether at 40/60 ratio) (× 1200)

There are 3 conditions which must be fulfilled before Mechanism A can operate. They are as follows: (1) the surfactants must be soluble in the oil phase in which it is initially placed; (2) the surfactants in the oil phase must solubilize or emulsify a part of the aqueous phase; and (3) a phase inversion must take place to form an O/W emulsion.

Further work using various oils and nonionic, anionic, and cationic surfactants resulted in no data contradictory to the proposed hypothesis. A careful analysis of the experimental data indicates that wherever any of the above 3 conditions were promoted, the emulsification efficiency improved. On the other hand, whenever a factor was introduced to hinder any of these conditions, the emulsification efficiency often dramatically decreased.

With regards to the first requirement of surfactant solubility in the oil phase, for example, an oil phase containing 14.3 per cent Tween 80/Arlacel 80 mixture at 80/20 ratio does not form a homogeneous phase. Upon standing, a surfactant-rich phase would separate from the mixture and settle to the bottom. The emulsion, prepared by quickly adding water to such a mixture with a moderate mixing, had coarse droplets and was unstable (Fig. 9(A)). However, by initially dispersing about 2 per cent of water in the oil phase, the mixture became homogeneous and the emulsion prepared improved remarkably as can be seen in Fig. 9(B).

The small amount of the water added to the above mentioned mixture apparently had a significant effect on the micellar structure in improving the solubility of the surfactant in the oil phase. Sometimes a similar effect could be achieved by adding a small amount of polar oils such as oleic acid. The result is also a definite improvement of emulsification efficiency.

Another example is a mixture of POE (10) oleyl ether/POE (2) oleyl ether at 40/60 ratio in mineral oil.* If an emulsion is prepared by immediately emulsifying the oil-surfactant mixture right after dispersion, a reasonably fine emulsion is obtained. However, if the oil-surfactant is allowed to stand overnight, it would separate into two layers—the lower oil layer containing most of the surfactant and the top oil layer containing much less surfactant. If an emulsion is prepared with such a two-layered oil phase, the emulsion would contain fine droplets derived from the lower surfactant-rich layer and coarse droplets originated from the upper, surfactant-poor layer. A microphotograph of such an emulsion revealing 2 distinct droplet size distributions is shown in Fig. 10.

The second requirement for the emulsification mechanism is related to the aqueous solubilization by the oil phase. From the experimental results presented so far, it is quite apparent that water solubilization must be related to emulsification efficiency. Other factors being equal, a larger quantity of water solubilization appeared to favor formation of a finer emulsion, although, the quantity of solubilization by itself cannot be regarded as an absolute measure of emulsification efficiency.

Although it is quite possible that a great water solubilization merely indicates the area of favorable condition for emulsification, there is also experimental evidence suggesting that solubilization is one of the necessary steps in the over-all emulsification process. In many systems studied, it was possible to improve emulsification by initially presolubilizing the water into the oil-surfactant mixture before emulsification. For example, a combination of 2- and 10-mole adducts of oleyl ethers in mineral oil forms a fairly complex solubilization diagram as shown in Fig. 11. When an emulsion was prepared in the usual manner using an 80/20 surfactant mixture indicated by a letter "X" in the diagram, the droplets were very coarse and the emulsion unstable. Subsequently, the emulsification procedure was slightly modified by first dispersing and solubilizing a small amount (2.6 per cent) of water into the oil phase to bring the mixture to point "Z" in the diagram. The resulting emulsion was very stable and had a very fine droplet size as shown in the photograph in Fig. 12 (Z).

Another similar presolubilized emulsification was carried out with a slightly reduced amount of initial water (2 per cent instad of 2.6 per cent) corresponding to point "Y" in the turbid area of Fig. 11. The result was an emulsion somewhat better than that of point X, but much inferior to the emulsion prepared at Z.

Since all three emulsions, X, Y, and Z have an identical, final composition, it must be concluded that the presolubilization treatment and the amount of the presolubilized water were positively affecting the emulsification process. In dispersing the water into this oil-surfactant mixture, it was noted that the water was not solubilized instantly, but it required time and considerable amount of mixing work before complete solubilization was obtained. This would suggest that, perhaps, the *rate of water solubilization* too is an important factor in emulsification.

It can be explained that when one starts emulsification from the point X by quickly adding water, even though, compositionwise, the mixture will pass points Y and Z, because of the very slow rate of solubilization, it is not possible for the mixture X to reach

*The total surfactant mixture was 14.3% in the oil phase.

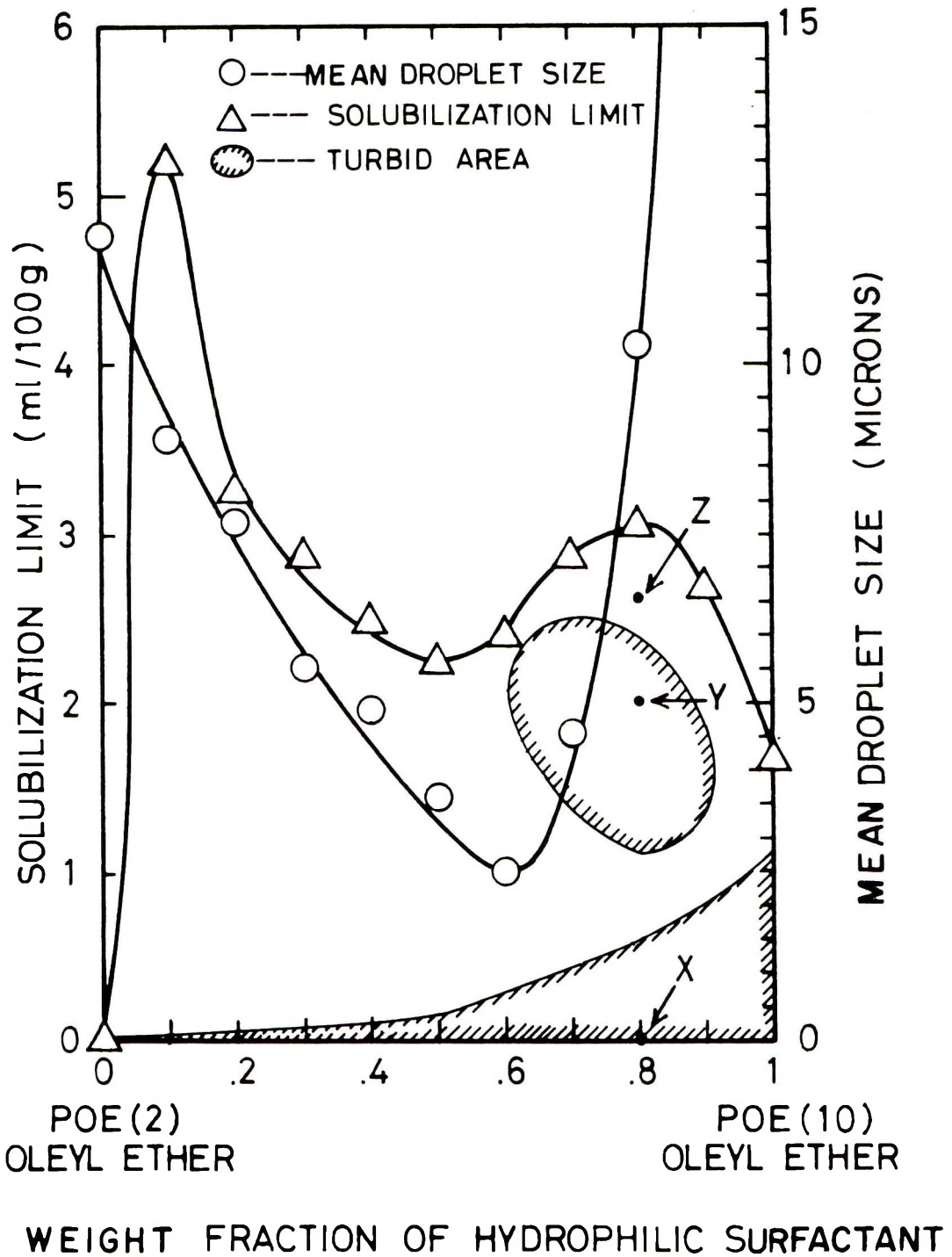


Figure 11. Complex solubilization diagram (emulsions contain 30 per cent oil phase, 65 per cent deionized water, and 5 per cent surfactant mixtures. Surfactant mixtures consist of hydrophilic POE (10) oleyl ether and lipophilic POE (2) oleyl ether at ratios indicated by abscissa)

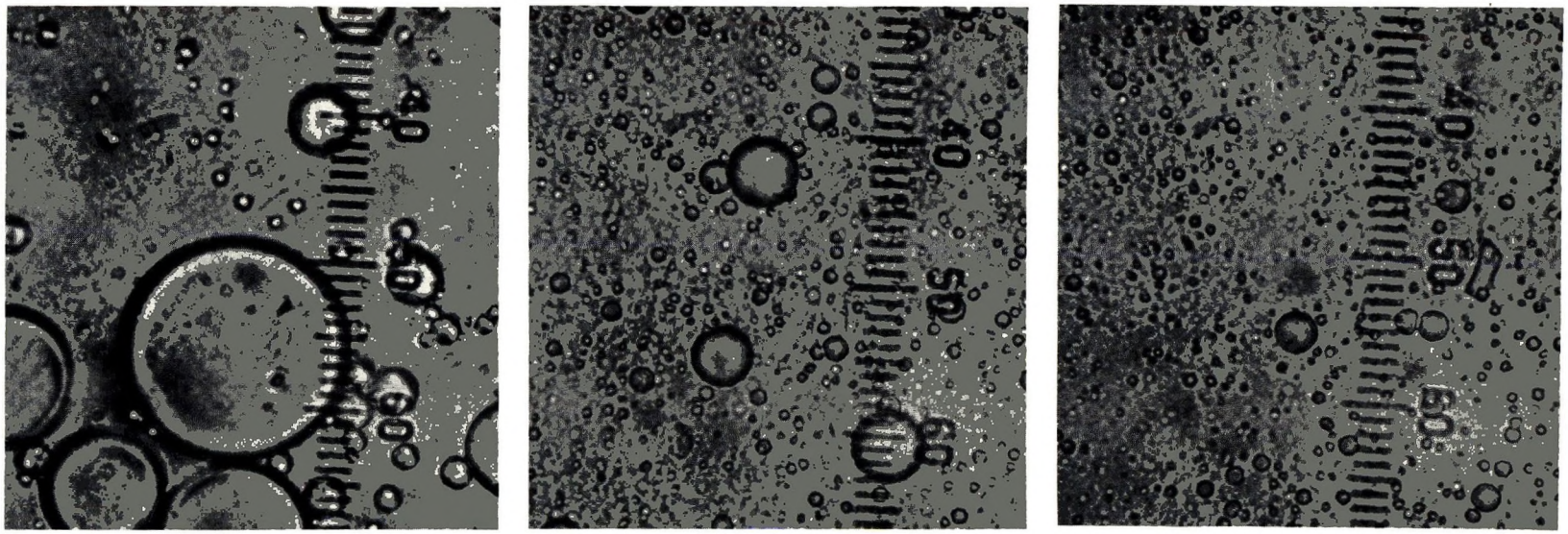


Figure 12. Microphotographs of emulsions prepared from 3 different points in Fig. 11

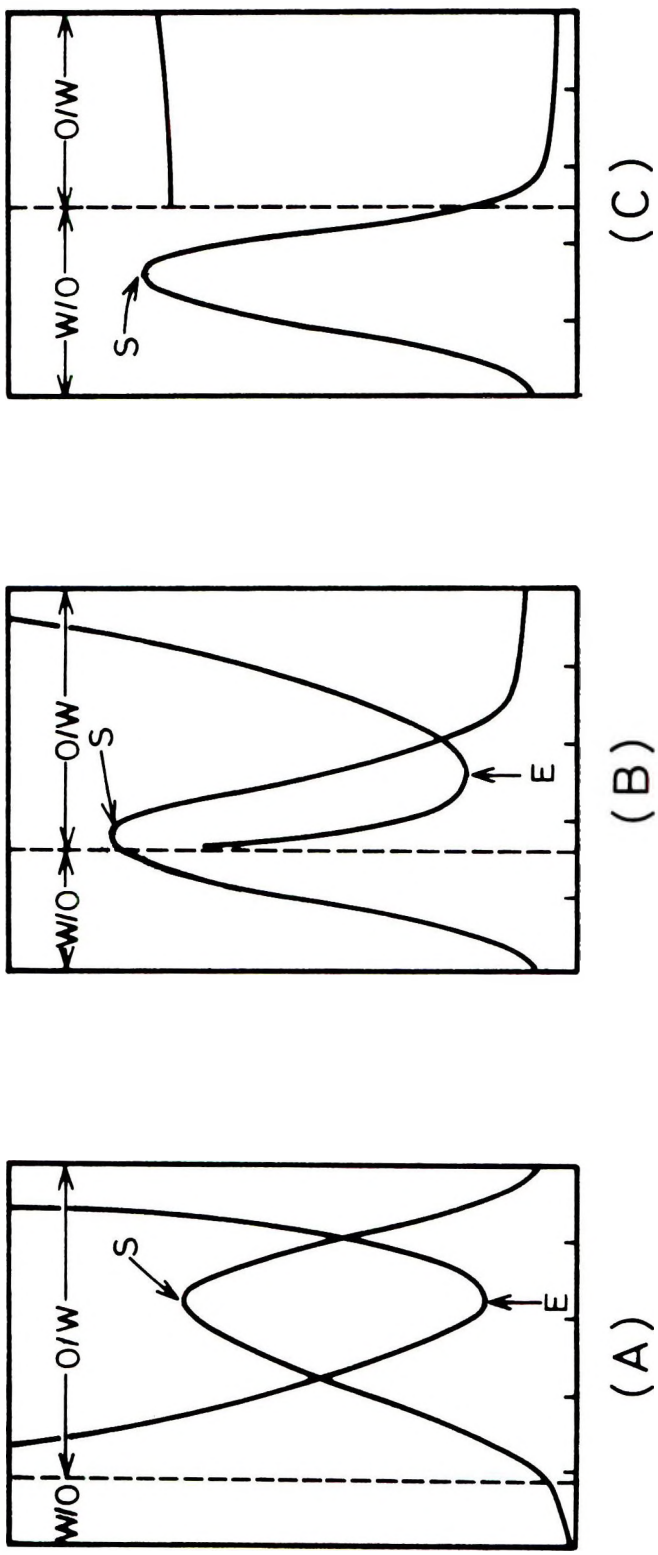


Figure 13. Effect of phase inversion boundary in relation to solubilization peak

the equivalent solubilized state of Z with the method of emulsification employed. With more added water, the hydrophilic surfactant soon migrates to the aqueous phase making it impossible for mechanism A to function.

The third requirement of mechanism A concerns phase inversion. In some systems, poor matching of the solubilization peak and the point of optimum emulsification were believed to be due to the phase inversion effect. As illustrated in Fig. 13 (A), phase inversion has no effect on the correlation when its boundary, indicated by the dashed line, is located on the left-hand side of the solubilization peak S. The optimum emulsification point E generally coincides with the peak in such a case. If the phase inversion boundary should fall on the peak as illustrated by Fig. 13 (B), the optimum emulsification point E generally shifts slightly to the right since an inverted W/O emulsion or mixed emulsion is formed at S. If the peak S occurs within the W/O region and the amount of solubilization is very small in the O/W region as illustrated by Fig. 13 (C), no optimum emulsification point exists as all O/W emulsions made have large droplet sizes.

It should be noted that phase inversion of an emulsion is dependent not only on the hydrophilic/lipophilic nature of the surfactants but also strongly on other variables such as internal phase volume, surfactant location, and the method of emulsion preparation (7, 10). Hence, the phase-inversion boundary can shift depending not only on the formulation, but also on the process variables such as the rate of addition of one phase to the other phase, degree of agitation, emulsification temperature, etc.

In 1964, the PIT (phase inversion temperature) method of selecting emulsifiers was suggested (11, 12) as an alternative to the HLB method. The PIT of an emulsion is dependent not only on the type of surfactants and oils, but also on other parameters such as phase volume, surfactant concentration, or the presence of salts. With regard to this, the PITs are said to provide more accurate information than the HLB, required HLB values which do not account for these effects. However, in practice, the PIT system, like HLB, also has shortcomings. First, systems containing anionic or cationic surfactants do not exhibit PIT and, therefore, the method would not apply. Second, since PIT is dependent on so many parameters, it is more complicated to apply it in a practical system than the HLB method. Finally, the PIT system is also only good as a rough guide, since it merely tells the formulator that he should not use combinations having PITs too close to the temperature at which the product is to be used or stored.

CONCLUSIONS

The obvious value of the solubilization-emulsification correlation here is its application in selecting emulsifiers for product development work. Since a solubilization measurement is relatively simple and the results are reproducible, it provides a quick way to determine the point of optimum emulsification. It can be also used to determine the effects of oil additives on emulsification, since the correlation holds not only for nonpolar oils, but also for many polar oils and their mixtures.

The solubilization and phase inversion data can also be very useful in process development work for emulsion products. They can be helpful in finding the best manufacturing method and also in avoiding manufacturing troubles.

For example, solubilization data obtained at various temperatures are useful in finding an optimum emulsification temperature. If the emulsification is done by the surfactant-in-oil method, it is well to study the oil phase containing various amounts of solubilized water at various temperatures. As it was pointed out earlier, the oil-surfactant mixture containing some water may not be stable and a separation into surfactant-rich and surfactant-poor phases can result in an emulsion with extremely nonuniform droplet size distribution. Therefore, consideration as to when and how rapidly to add the aqueous phase to the oil phase may become a very important factor in preventing manufacturing difficulties.

The method of solubilization measurements used in this work relied upon visual observations and the solubilization limit was defined as the point beyond which a permanent turbidity would develop upon addition of more water. This method is very simple to use, but it does have some disadvantages. In some systems, turbidity does not develop sharply, resulting in a difficulty in determining the endpoint. Another problem is that if the mixture is not completely transparent at the temperature of measurements, it would be very difficult or impossible to judge the endpoint. This would rule out the application of the method to oil mixtures containing two immiscible oils (e.g., mineral oil and silicone fluids) or to the mixture containing a solid suspension.

However, it is believed that such difficulties can be overcome by using other means of determining solubilization. One promising method is the use of vapor pressure measurements which has been successfully used in measuring solubilization of water in nonaqueous systems (14, 15). The vapor pressure of an oil containing solubilized water generally shows an increase with increasing amount of solubilized water until the maximum point is reached. Since the method is not dependent upon a visual observation, the previously mentioned difficulties would not occur.

Unlike emulsion stability which is extremely difficult to define, solubilization is a better-defined phenomenon and can be related to the physical and chemical properties of the materials involved. Therefore, it is believed that the correlation presented here can be a very valuable basis for developing a useful tool for emulsifier selection, which is more accurate and reliable than other existing methods.

ACKNOWLEDGMENT

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Society of Cosmetic Chemists Award Sponsored by the Miranol Chemical Company

The Society of Cosmetic Chemists Award sponsored by the Miranol Chemical Co., Inc., was presented to Douglas Howes, Unilever Research Laboratory, for his outstanding achievements in the study of the precutaneous absorption of surfactants and the correlation of this absorption with skin irritation.

An inscribed scroll and a $2,000 honorarium were presented formally by Dr. Karl Laden, Society of Cosmetic Chemists President, at the Awards Luncheon held May 5, at the Hotel Bonaventure in Montreal, Canada.

Left to right: Dr. Karl Laden, SCC President; Douglas Howes, Unilever Research Laboratory, Awardee

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Diffusion theory analysis of transepidermal water loss through occlusive films

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Received January 25, 1977.

Synopsis

It is shown that simple DIFFUSION THEORY dictates that the application of an OCCLUSIVE FILM on SKIN always results in a decrease in TRANSEPIDERMAL WATER LOSS (TWL), as expected intuitively. The basic inconsistency in a previous analysis, which seemed to predict the possibility of the opposite effect, is pointed out.

INTRODUCTION

In a recent paper in this Journal (1), a theoretical argument was advanced to demonstrate that an occlusive film, when applied to skin, may lead not only to increased hydration of the stratum corneum but, contrary to expectation, to a concurrent *increase* in the transepidermal water loss (TWL). The authors used their argument to explain some experimental data that seemed to indicate such an increased flux, and to caution against rejecting potential occlusive agents that exhibit this effect, since they may, nevertheless, be excellent in their ability to effect increased skin hydration. The authors went so far as to state that "this increase in TWL is evidence of increased skin hydration in the stratum corneum."

Although the analysis seemed sound at first sight, we had the distinct impression that the conclusion had to be in violation of some basic principles in transport phenomena. If not, some curious paradoxes could be envisaged (for example, insulating one's house could conceivably lead to a greater heat loss in wintertime). The question to be asked is whether introduction of an extra resistance in a transport process can cause a change in the original resistance that will not only nullify, but overcompensate for, the intrinsic effect of the added resistance. We believe that such an effect is, in general, impossible, although we shall prove it only, in a very simple way, for the system of an occlusive film on skin.

THEORETICAL

Let us consider the concentration (or activity) profile of water in the stratum corneum in the absence and presence of an occlusive film (Fig. 1). In both cases, the concentra-

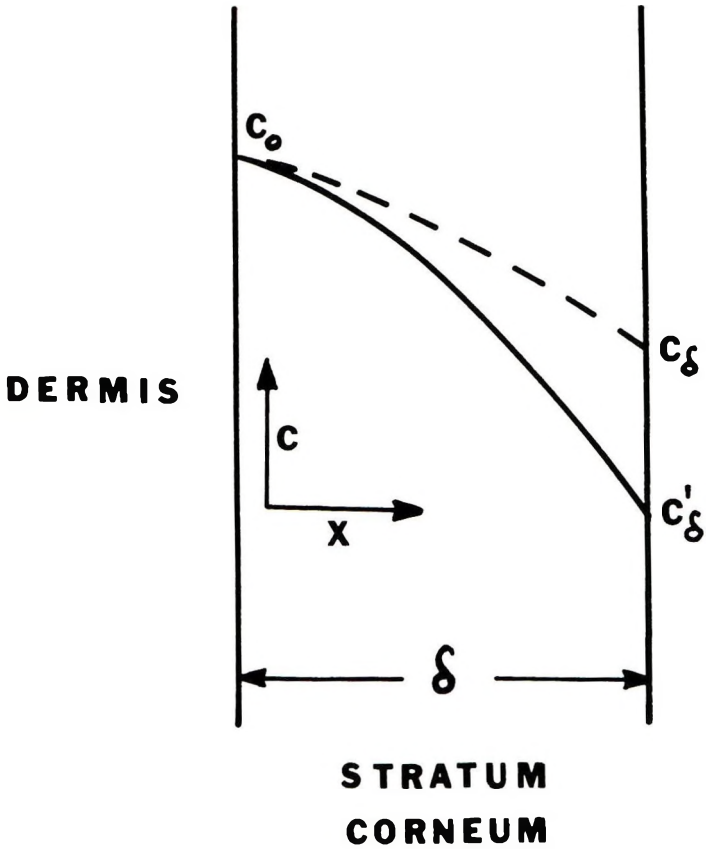

Figure 1. Concentration profile of water in the stratum corneum: solid line, nonoccluded case; dashed line, occluded case

tion at the dermis side equals c_o, which is determined by the constant activity of water in the dermis. In the nonoccluded case, the concentration drops to c'_δ at the outer surface ($x = \delta$), which is at equilibrium with the ambient atmosphere. Therefore, c'_δ is determined by the ambient water activity. In the occluded case, the concentration drops only to c_δ ($c_\delta > c'_\delta$), since part of the overall activity drop has to occur across the occlusive film (not shown in Fig. 1). Thus, the water content of the stratum corneum is indeed raised by the presence of an occlusive film, namely by an amount equal to the area between the two curves in Fig. 1.

It is an essential feature of Fig. 1 that the concentration profile is not linear, but curved as a result of the concentration dependence of the diffusion coefficient D(c). At any point in the corneum, the water flux is given by

$$J = -D(c)\frac{dc}{dx} \tag{1}$$

or upon integration,

$$\int_0^\delta J\,dx = -\int_{c_0}^{c_\delta} D(c)\,dc \tag{2}$$

In the steady state, J does not depend on x, so that

$$J\delta = -\int_{c_0}^{c_\delta} D(c)dc = \int_{c_\delta}^{c_0} D(c)dc \quad \text{(occluded case)} \tag{3}$$

and

$$J'\delta = -\int_{c_0}^{c'_\delta} D(c)dc = \int_{c'_\delta}^{c_0} D(c)dc \quad \text{(nonoccluded case)} \tag{4}$$

Hence, the difference in flux is given by

$$J' - J = \frac{1}{\delta}\left[\int_{c'_\delta}^{c_0} D(c)dc - \int_{c_\delta}^{c_0} D(c)dc\right] = \frac{1}{\delta}\int_{c'_\delta}^{c_\delta} D(c)dc \tag{5}$$

Since c_δ is always greater than c'_δ, and D(c) is greater than zero, the integral on the right-hand side will always be positive, whatever the form of D(c), which leads to the general conclusion that

$$J' > J \tag{6}$$

i.e., the occlusive film always results in a decrease in water loss rate, as expected intuitively.

As in (1), the assumption was made that the corneum thickness, δ, does not change as a result of increased hydration; however, we know that swelling does take place. This effect can only further increase the difference between J′ and J. It should be noted also that the use of activities instead of concentrations in the above analysis in no way modifies the result.

It is clear now where the analysis in (1) went astray. It assumes, and quite rightfully so (2), that the diffusion coefficient increases with increasing concentration of water in the corneum. However, in their analysis, the authors consider "D to be constant for each membrane, even though this may not be the case for nonuniformly hydrated stratum corneum." This basic internal inconsistency gives rise to the paradox.

It is not our intention to dispute the validity of the experimental data quoted in (1). But a different mechanism would have to be found to explain such findings. Other data exist that appear to violate the straightforward diffusion theory. For example, the maximum in the relationship between TWL and ambient relative humidity, as reported by Grice *et al.* (3) for the *in vivo* situation, cannot be explained this way. However, other *in vivo* (4), as well as *in vitro* (5,6), data do show the expected continuous increase of flux with increasing RH difference across the corneum. In this connection, it may be pointed out that *in vivo* measurements are notoriously variable and sensitive to extraneous influences.

CONCLUSION

A truly occlusive film, when applied to skin, can only reduce the rate of TWL. When the opposite effect is found in practice, the conclusion must be that the agent applied is not simply occlusive (i.e., inert) but must interact in a more complex way with the stratum corneum.

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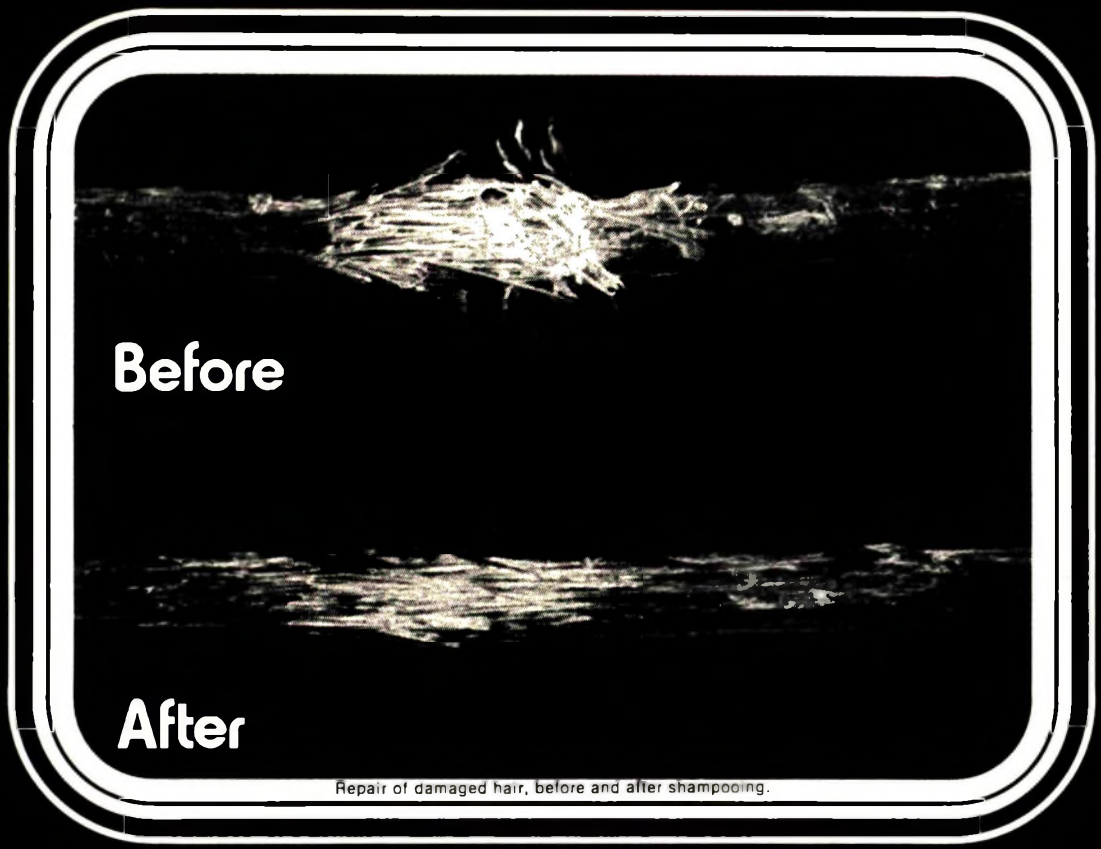

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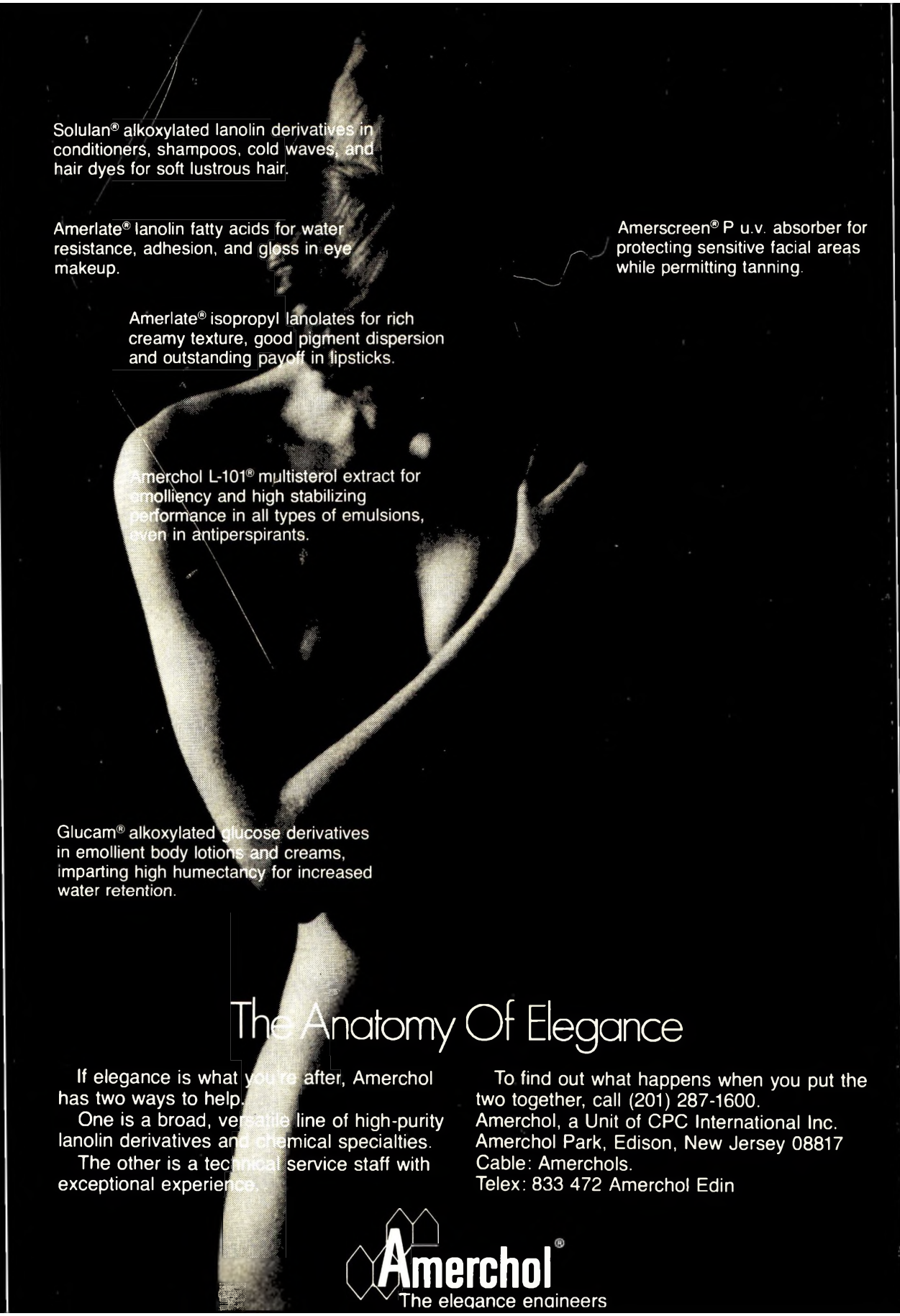
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